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I. M. ARIAS 510

Of three members of a family with familial non-hemolytic jaundice associated with conjugated bilirubin in the serum, two had pigment in the liver cells (Dubin-Johnson syndrome), one did not and thus fell into the category described by Rotor. Except for the difference in hepatocellular (lysosomal) pigment deposition, all three members of the family gave very similar results in all parameters of hepatic function examined. It is therefore suggested that the Dubin-Johnson and Rotor syndromes reflect quantitative rather than qualitative variations in an inborn error affecting transport of bilirubin and other compounds from the liver cells into the bile.

Ineffective Erythropoiesis . . . . FARID I. HAURANI AND L. M. TOCANTINS 519

A factor in the appraisal of anemic states which often is neglected is what here is called "ineffective erythropoiesis," by which is meant the discrepancy between total red cell (or hemoglobin) mass in the peripheral circulation and the total quantity of red cells produced in the bone marrow and extramedullary sites, unexplained by blood loss due to hemorrhage or hemolysis. Appropriate erythrokinetic studies to estimate this discrepancy revealed it to be sizable in some anemic states, such as thalassemia major, extramedullary hemopoiesis, refractory normoblastic anemia and megaloblastic anemia, but inappreciable in others, such as the hemoglobinopathies, aplastic anemia and chronic myeloid leukemia. The implications are discussed informatively.

Syndrome of Iron Deficiency Anemia, Hepatosplenomegaly, Hypogonadism, Dwarfism and Geophagia
ANANDA S. PRASAD, JAMES A. HALSTED AND MANUCHER NADIMI 532

An interesting account of a syndrome noted in young Iranian males involving iron deficiency anemia, marked hepatosplenomegaly, dwarfism with hypogonadism, associated with malnutrition and prolonged clay eating, and responsive to oral iron therapy and balanced diet. It could be shown convincingly that the marked iron deficiency was not due to blood loss, and that the diet, chiefly wheat bread, contained adequate amounts of iron which was not, however, adequately absorbed, in part perhaps due to the ingestion of clay. The possibility of an associated zinc deficiency also is considered.

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A Comparison of Laboratory Methods for the Control of Anticoagulant Therapy with Prothrombinopenic Agents. I. The Quick One-Stage Procedure, the Prothrombin and Proconvertin Test and the One-Stage Determ nation of True Prothrombin Activity

THEODORE RODMAN, BERNARD H. PASTOR AND KENNEDY C. FAWCETT 547

II. Problems Encountered in the Laboratory Control of Anticoagulant Therapy with the One-Stage Determination of Prothrombin Complex Activity

THEODORE RODMAN, BERNARD H. PASTOR AND BERTHA L. HOXTER 555

The Quick one-stage procedure has long been widely employed, despite certain inadequacies, for estimation of prothrombin complex activity to control anticoagulant therapy. The first paper compares results obtained with the Quick one-stage test (Link-Shapiro modification, using Simplastin® in one group, Acuplastin® in another) with the results obtained with more elaborate tests designed to give better estimates, namely, Owren's P and P test and his one-stage determination of true prothrombin activity. The findings indicate that, for the purpose, the Quick one-stage procedure, if properly performed with standardized technics and materials, gives satisfactory results. Until more is known about which specific factors are most critical for effective anticoagulation, the Quick test is probably preferable as a routine procedure. The second paper examines the reasons for the startlingly wide variation in results of the Quick one-stage test as performed in different laboratories. Three major sources of confusion were discovered. One has to do with the use of different thromboplastin preparations; another with the variation in diluents and diluent curves in converting plasma clotting time to per cent of normal plasma activity; the third concerns carelessness in overexposing plasma and reagents to higher temperatures in the water bath.

Fibrinolysis Induced by Pressor Amines

EDWARD GENTON, FRED KERN, JR. AND KURT VON KAULLA 564

Among the hazards of therapy with pressor amines is their tendency to increase fibrinolytic activity and thus aggravate bleeding. This is clearly brought out in the present study which demonstrates activation of fibrinolysis of about equal degree by epinephrine, norepinephrine and phenylephrine in normal human subjects. There was no close correlation between the vasopressor action of these drugs and their effect on fibrinolysis.

Serum Globulin Deficiencies in Non-Tropical Sprue, with Report of Two Cases of Acquired Agammaglobulinemia

KENNETH A. HUIZENGA, ERIC E. WOLLAEGER, PAUL A. GREEN AND BERNARD F. MCKENZIE 572

It would appear that some 20 per cent of patients with acquired agammaglobulinemia also exhibit a sprue-like syndrome, and that in some patients with non-tropical sprue hypogammaglobulinema develops, with or without hypoalbuminemia. The authors cite two cases falling into the latter category. It is suggested that faulty intestinal absorption may be responsible for impaired synthesis of gamma globulin in such cases.

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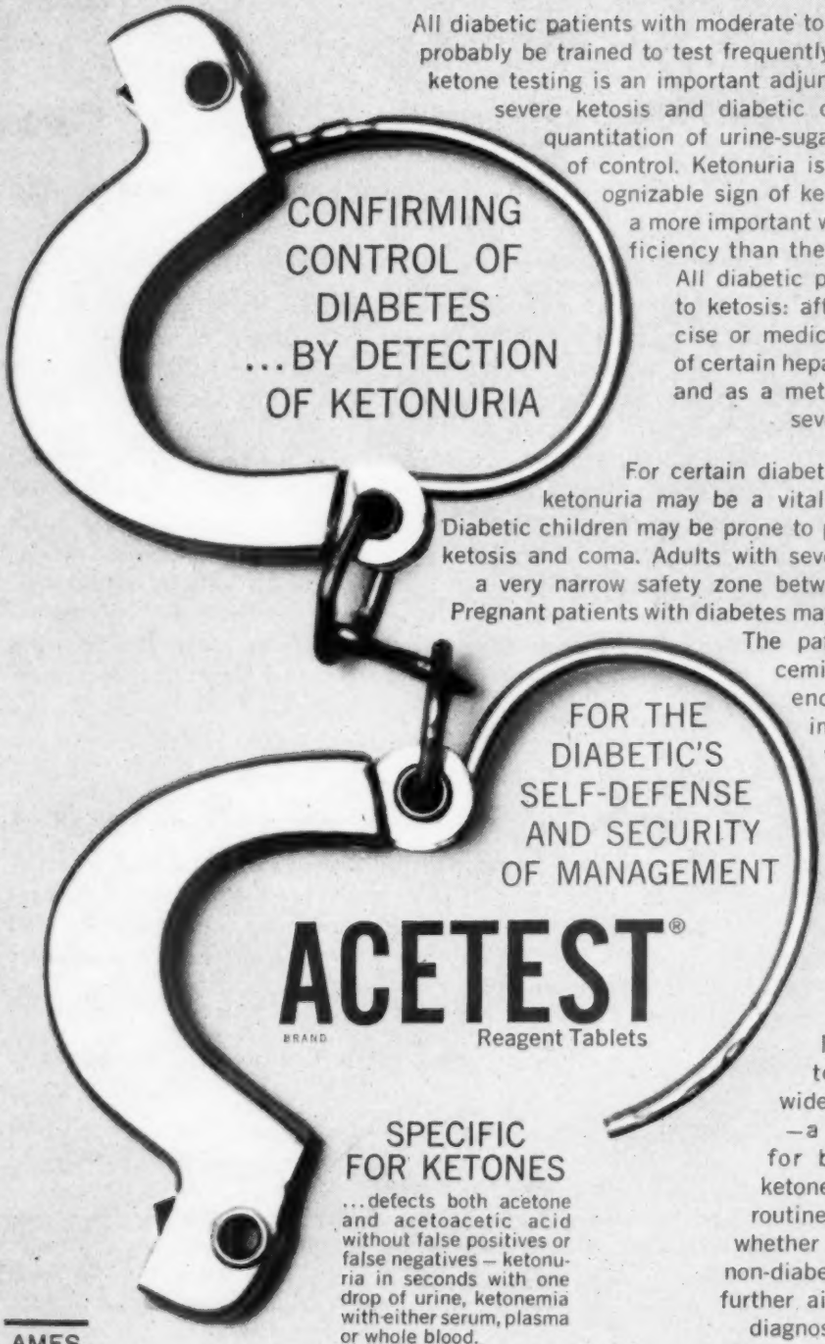

CONFIRMING CONTROL OF DIABETES ...BY DETECTION OF KETONURIA

All diabetic patients with moderate to severe diabetes should probably be trained to test frequently for ketonuria. Routine ketone testing is an important adjunct in the prevention of severe ketosis and diabetic coma, just as frequent quantitation of urine-sugar indicates the degree of control. Ketonuria is not only the first recognizable sign of ketosis,[1] but also may be a more important warning of insulin-insufficiency than the degree of glucosuria. All diabetic patients can be subject to ketosis: after errors of diet, exercise or medication; in the presence of certain hepatic and renal disorders; and as a metabolic consequence of severe infection or stress.

For certain diabetic patients, testing for ketonuria may be a vital part of daily routine. Diabetic children may be prone to precipitous episodes of ketosis and coma. Adults with severe diabetes may have a very narrow safety zone between control and coma. Pregnant patients with diabetes may easily become ketotic. The patient on oral hypoglycemic therapy may experience drug failure, need insulin temporarily or develop unwise habits of diet or medication—ample justification for his self-defense with routine testing for ketonuria.

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(1) Duncan, G. G.: Diseases of Metabolism, ed. 4, Philadelphia, Saunders, 1959, p. 795.
(2) Lee C. T., and Duncan G. G.: Metabolism 5:144, 1956.

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Antirheumatic Potency of Chemically Modified Adrenocortical Steroids
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The adrenocortical steroids have been extensively studied from the point of view of structure-activity relationships, and from these studies have come some interesting correlations which do not, however, throw much light on how they exert their remarkable antirheumatic properties. This activity must be assayed empirically, as in the present study which compares the antirheumatic potency of thirty-two analogs of hydrocortisone and cortisone. Some of these compounds have proved to be sufficiently advantageous to be made available commercially, and are well known; others have found no place in therapy.

Review

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If the title of this essay on oncology looks unpromising in this age of dynamic approach to mechanisms of disease, the reader is in for a pleasant surprise. Dr. Grigg shows us again that looking back upon the speculations of the medical past—and this is done in a masterly manner—can be quite as interesting and exciting as looking forward to the speculations of the future. In the process, one discovers much that is new about the old-fashioned tumor which is the subject of the review.

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Xanthomatous Biliary Cirrhosis Following Chlorpromazine
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RACHMIEL LEVINE, M.D., *Guest Editor*

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1. Berger, F. M., and Margolin, S.: A Centrally Acting Blood Pressure Lowering Agent (W-583). Fed. Proc. 20:113 (March) 1961. 2. Diamond, S., and Schwartz, M. Scientific Exhibit at Ill. State Med. Soc. Chicago, (May) 1961. 3. Douglas, J. F., Ludwig, B. J.,, Ginsberg, T. and Berger, F. M.: Studies on W-583 Metabolism. Fed. Proc. 20:113 (March) 1961. 4. Duarte, C., Brest, A. N., Kodama, R., Naso, F., and Moyer, J. H: Observations on the Antihypertensive Effectiveness of a New Propanediol Dicarbamate (W-583). Curr. Ther. Res., 2:148-52 (May) 1960. 5. DuChez, J. W., Scientific Exhibit at Amer. Academy of Gen. Practice, Miami, (April) 1961. 6. Kletzkin, M., and Berger, F. M.: A Centrally Acting Antipressor agent. Fed. Proc. 20:113 (March) 1961. 7. Mulinos, M. G., Scientific Exhibit at Amer. Coll. Card. New York, (May) 1961. 8. Mulinos, M. G., Saltefors, S., Boyd, L. J. and Cronk, G. A.: Human Pharmacology Studies with W-583. Fed. Proc. 20:113 (March) 1961. 9. Shubin, H., Scientific Exhibit, Amer. Coll. Card. New York, (May) 1961.

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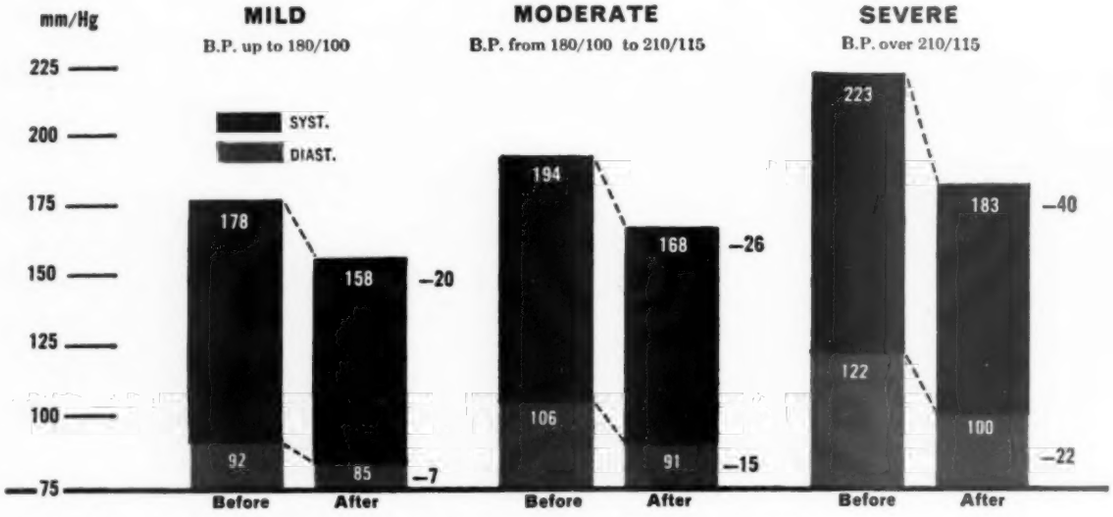

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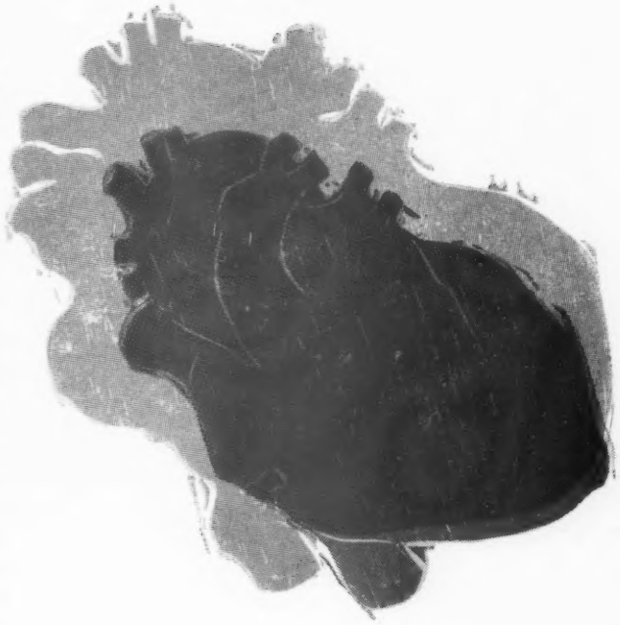

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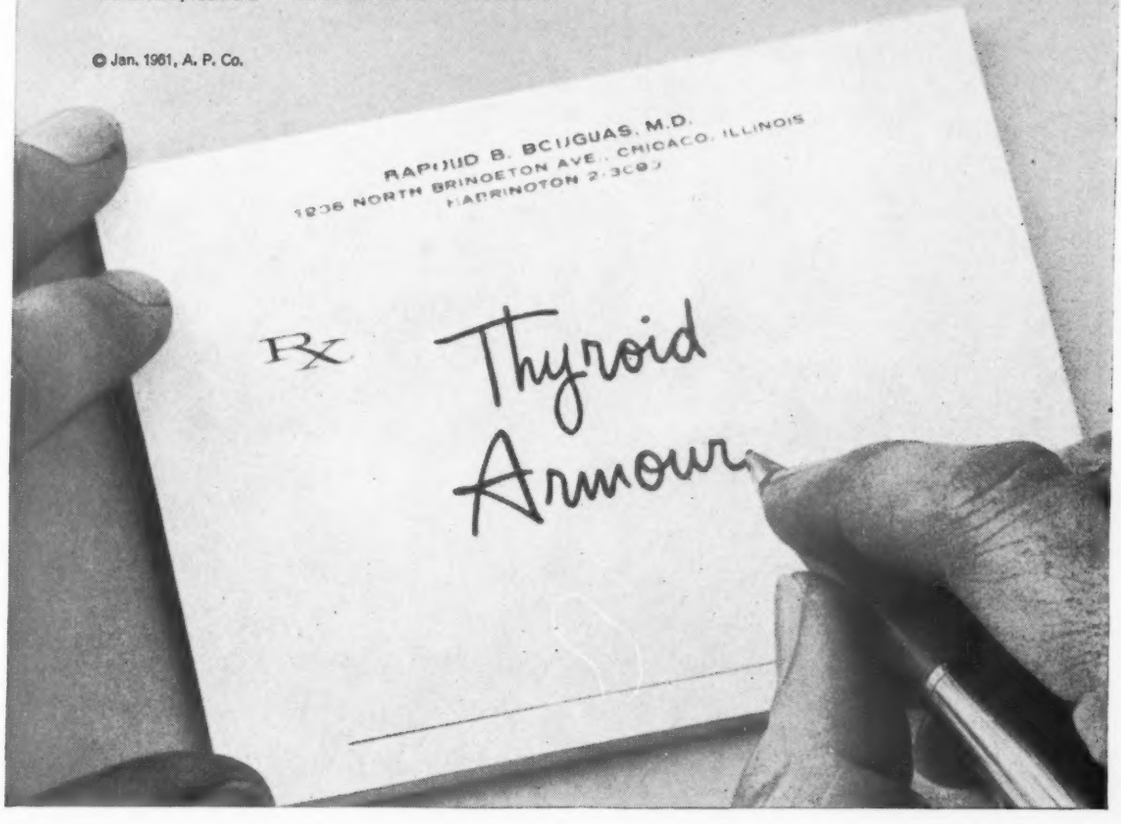
It takes only 2 seconds to specify "THYROID ARMOUR" on a prescription blank, yet these words represent the highest grade thyroid available, manufactured with all the control skills learned during three-quarters of a century of experience with endocrine products. THYROID ARMOUR is the original standard of comparison for all thyroid preparations, and is regarded throughout the world as the quality thyroid product.

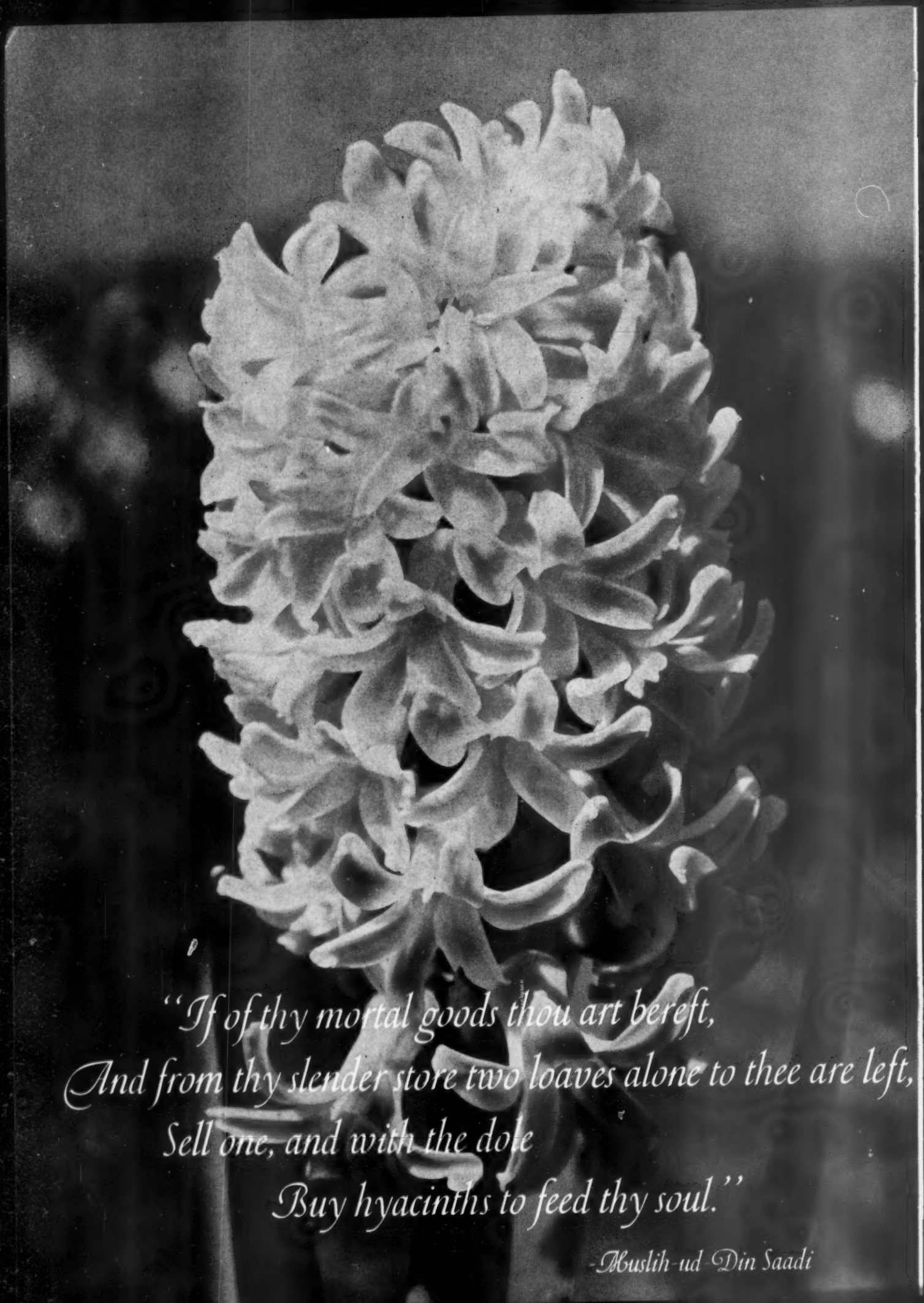
THYROID U.S.P.

Thyroid Tablets (Armour) are prepared from fresh selected glands, desiccated and standardized by official U.S.P. method to contain 0.2 per cent of iodine in thyroid combination. Thyroid Powder U.S.P. (Armour) is standardized and of uniform potency. USES: Thyroid deficiencies, cretinism, myxedema, nodular goiter (non-toxic), non-nodular goiter. A variety of clinical conditions will respond to the use of Thyroid (Armour) when subclinical hypothyroidism is involved, i.e., gynecologic conditions such as functional menstrual disorders, sterility, habitual abortion; recurring conjunctivitis; certain types of anemias and obesity; and certain changes which occur in hair, skin and fingernails. DOSAGE: ¼ to 5 grains daily as required by clinical condition. Therapeutic effect develops slowly and lasts for two months or longer. Thus the daily dose may be given as a single dose (preferably in the morning) rather than several times daily. Patients treated with thyroid should be continuously under the physician's observation. CONTRAINDICATIONS: Heart disease and hypertension, unless the metabolic rate is low. SUPPLIED: Tablets—bottles of 100, 1000 and larger: potencies of ¼, ½, 1, 2 and 5 grains. Powder—1 oz. 4 oz., and 1 lb. bottles.

ARMOUR PHARMACEUTICAL COMPANY
KANKAKEE, ILLINOIS *Armour Means Protection*

© Jan. 1961, A. P. Co.




"If of thy mortal goods thou art bereft,
And from thy slender store two loaves alone to thee are left,
Sell one, and with the dole
Buy hyacinths to feed thy soul."
-Muslih-ud-Din Saadi

Upjohn

75th year

Man does not live by bread alone.
If he did, medicine would be purely a science, concerned only with "bread to nourish the body."

Thoughtful physicians have long recognized the equal essentiality of "hyacinths to feed the soul." This is the *art* of medicine.

If yours is a typical practice, many of the patients who come to you have no demonstrable somatic pathology. Yet their symptoms often are myriad: low back pain, recurrent headaches, insomnia, anorexia, chronic fatigue, apathy, inability to concentrate, "blues."

Most of these patients are not candidates for psychiatry, and certainly not for tranquilizers or sedatives. They are candidates for the simple psychomotor effect of Monase. Tests in more than 2,000 such patients justify the expectation that Monase will enable many of these patients to sleep better, eat better, and feel better.

For the 4 out of 10 patients with no demonstrable pathology,† consider

Monase*

*TRADEMARK, REG. U.S. PAT. OFF.
†ESTIMATED AVERAGE IN GENERAL PRACTICE
COPYRIGHT, 1961, THE UPJOHN COMPANY

Description: Monase is etryptamine acetate, a unique non-hydrazine compound, developed in the Upjohn Research Laboratories.

Indications: Various depression states: manic-depressive reaction, depressed type; involutional psychotic reactions with depressed features; psychotic depressed reactions; psychoneurotic depressive reactions; psychiatric disorders with prominent depressive symptoms or features; transient situational personality disorders with pathological depressive features.

Dosage: 30 mg. daily in divided doses. Initial benefit may be observed within 2-3 days, but maximum results may not be apparent until after 2 or more weeks. Adjustment of dose to individual response should be effected in increments or decrements of 15 mg. daily at weekly intervals. The daily maintenance dose ranges between 15 and 45 mg. In schizophrenics, 30 mg. daily may be useful as an adjunct in activating these patients or brightening their mood.

Contraindications and Precautions: There are no known absolute contraindications to Monase therapy. However, the drug should be used with caution in schizoid or schizophrenic patients, paranoids, and in patients with intense anxiety, as it may contribute to the activation of a latent or incipient psychotic process. Patients with suicidal tendencies should be kept under careful observation during Monase therapy until such time as the self-destructive tendencies are brought under control.

Patients who are on concomitant antihypertensive therapy should be watched carefully for possible potentiation of hypotensive effects. Added caution should be employed in patients with cardiovascular disease in view of the occasional occurrence of postural hypotension, and the possibility of increased activity as a result of a feeling of increased well being.

Despite the fact that liver damage or blood dyscrasias have not been reported in patients receiving Monase, as is the case with any new drug, patients should be carefully observed for the development of these complications. Monase should probably not be used in patients with a history of liver disease or abnormal liver function tests. Also the usual precautions should be employed in patients with impaired renal function, since it is possible that cumulative effects may occur in such patients.

Monase should be employed with caution in patients with epilepsy since the possibility exists that the epileptic state may be aggravated. Also because of its autonomic effects, therapy with Monase may aggravate glaucoma or may produce urinary retention. Monase must not be administered concomitantly with imipramine. In patients receiving Monase caution should be employed in administering the following agents or related compounds in view of possible lowering of the margin of safety: meperidine, local anesthetics (procaine, cocaine, etc.), phenylephrine, amphetamine, alcohol, ether, barbiturates or histamine.

Toxicity and Side Effects: The side effects observed in patients on Monase therapy in general have been mild and easily managed by symptomatic therapy or dose reduction. If such side effects persist of are severe, the drug should be discontinued. Alterations in blood pressure, usually in the form of postural hypotension, or more rarely, an elevation of blood pressure have been reported. Other side effects include allergic skin reactions and drug fever and those that appear to be dose related since they are more likely to occur when the daily dose exceeds 60 mg. These are nausea and gastrointestinal upset, headache, vertigo, palpitation, dryness of the mouth, blurred vision, over-stimulation of the central nervous system, restlessness, insomnia, paradoxical somnolence and fatigue, muscle weakness, edema, and sweating. Following sudden withdrawal of medication in patients receiving high doses for a prolonged period. There may occur a "rebound" withdrawal effect which is characterized by headache, central nervous system hyperstimulation and occasionally hallucinations.

Supplied: 15 mg. compressed tablets in bottles of 100 and 500.

clinical experience continues to indicate value of the CYTOTOXIC AGENT...

CYTOXAN®

Cyclophosphamide, Mead Johnson

for palliative chemotherapy of certain types of malignant neoplasms

"Cyclophosphamide [Cytoxan] has proved a valuable addition to chemotherapeutic drugs available for the treatment of malignant diseases of the haemopoietic and reticuloendothelial systems.... Particularly effective in Hodgkin's disease, lymphosarcoma, chronic lymphocytic leukaemia, and myelomatosis...."[1]

"Objective data suggest that this agent [Cytoxan] has advantages not possessed by standard alkylating agents now in clinical use."[2]

"With the use of cyclophosphamide [Cytoxan] there is a relative lack of thrombocytopenia and a diminution in gastrointestinal side-effects, so that it may offer therapeutic advantages over other alkylating agents."[3]

Other Advantages in Clinical Practice: Broad-spectrum application. High therapeutic index. No vesicant activity—may be given orally or parenterally.

(1) Matthias, J. Q.; Misiewicz, J. J., and Scott, R. B.: Brit. M. J. *2*:1837-1840 (Dec. 24) 1960.
(2) Coggins, P. R.; Ravdin, R. G., and Eisman, S. H.: Cancer *13*:1254-1260 (Nov.-Dec.) 1960.
(3) Papac, R.; Petrakis, N. L.; Amini, F., and Wood, D. A.: J.A.M.A. *172*:1387-1391 (March 26) 1960.

DOSAGE: ***For neoplasms relatively susceptible to Cytoxan*** — Patients with lymphomas and other neoplasms believed to be relatively susceptible to Cytoxan therapy are given an initial dose of 2-3 mg./Kg./day intravenously. White blood counts and platelet determinations should be made daily or twice weekly and the dosage adjusted accordingly. Intravenous infusions should be continued for at least 6 days unless otherwise indicated. A leukopenia of between 1500 and 5000 cells per cu. mm. (or lower) may be expected between the tenth and fourteenth day. In the presence of a leukopenia of less than 2000/cu. mm. Cytoxan should be discontinued until the white cell count returns to 2000 to 5000 (usually within a week). Dosage is subsequently adjusted as indicated by the patient's objective response and the leukocyte count. If the patient is subjectively improved, if the size of the tumor has decreased, or if the white cells are satisfactorily maintained between 2000 and 5000/cu. mm. oral dosage may be instituted equivalent to intravenous dosage.

Thrombocytopenia is rarely observed on this regimen. If platelet counts of less than 100,000/cu. mm. are observed, the patient should be watched carefully. If platelets continue to decrease, Cytoxan should be discontinued.

The patient who has had previous treatment with alkylating agents, or x-ray, or is debilitated may be more susceptible to bone marrow depression, and initial Cytoxan doses should be more conservative than the above. Such patients should have more frequent hematologic evaluation. Good medical practice demands access to a reliable hematologic laboratory when using Cytoxan.

For neoplasms relatively resistant to Cytoxan—Patients with carcinomas and other malignant neoplasms believed to be less susceptible to Cytoxan therapy are given a dose of 4 to 8 mg./Kg./day intravenously. Unless there are indications to the contrary, this dose is continued for 6 days, then stopped. Leukopenia usually ensues on the tenth to fourteenth day after the first dose of Cytoxan. Thrombocyte reduction is not common, and platelets may actually increase. The leukocyte count promptly returns toward normal levels in most cases, and as it begins to increase, sufficient Cytoxan is administered to maintain it near 2000 to 5000/cu. mm. This may be accomplished by two intravenous injections weekly, or by oral administration, or by a combination of both routes. An oral dosage of 50 to 200 mg. daily or an intravenous injection of 5 mg./Kg. twice weekly will usually suffice.

The platelet and leukocyte counts should be followed carefully, and the prior treatment history of patients carefully evaluated as delineated above.

Leukopenia as a guide to adequacy of dosage—The best objective measure for dosage seems to be the number of circulating white blood cells. This is used as an index of the activity of the hematopoietic system, especially the bone marrow. The mechanism by which Cytoxan causes a reduction in the level of white blood cells is not known, but cessation of dosage results in an increase in the level, indicating that the hematopoietic system had not been permanently affected. When large doses (8 mg./Kg./day for 6 days) are given initially, the white cell count falls rapidly. Following the cessation of the 6-day course, the white cells may continue to decline for as long as 8 days and then increase. The reduction of the white cell count during Cytoxan therapy and its subsequent increase when therapy is discontinued can be repeated in the same patient. Maximal reduction in leukocyte count indicates the maximal permissible Cytoxan level for therapeutic effect. Leukopenic patients must be watched carefully for evidence of infection.

Total white blood cell and thrombocyte counts should be obtained 2 or more times weekly in order to evaluate therapy and to adjust dosage.

SIDE EFFECTS: Although Cytoxan is related to nitrogen mustard, it has no vesicant effect on tissue. It does not traumatize the vein when injected intravenously, nor does it cause any localized tissue reaction following extravasation. It may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally or directly into the tumor, when indicated. It is apparently active by each of these routes.

Nausea and vomiting are common and depend on dose and on individual susceptibility. However, many investigators accept the nausea and vomiting in favor of maintaining maximal therapy. The vomiting can be controlled with antiemetic agents.

Alopecia is a frequent side reaction to Cytoxan therapy. It has been observed in 28% of the patients studied in this country. The incidence is greater with larger doses. The loss of hair may first be noted about the 21st day of therapy and may proceed to alopecia totalis. This effect is reversed following discontinuance of Cytoxan; during reduced maintenance therapy, hair may reappear. It is essential to advise the patient in advance concerning this effect of the drug.

Dizziness of short duration and of minor degree has occasionally been reported.

Leukopenia is an expected effect and can be used as a guide to therapy. Thrombocytopenia may occur, especially after large doses. The leukocyte or platelet counts of an occasional patient may fall precipitously after even small doses of Cytoxan, as with all alkylating agents. The drug should be discontinued in such patients and reinstituted later at lower dosage after satisfactory hematologic recovery has occurred. Prior treatment with x-ray or with other chemotherapeutic agents frequently causes an earlier or exaggerated leukopenia or thrombocytopenia after Cytoxan medication. Only rarely has there been a report of erythrocyte or hemoglobin reduction.

ADMINISTRATION: Add 5 cc. sterile water (Water for Injection, U.S.P.) to 100 mg. of Cytoxan in the sterile vial (add 10 cc. to 200 mg. vial). Shake, allow to stand until clear, remove with sterile syringe and needle and inject.

The freshly prepared solution of Cytoxan may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally, or directly into the tumor. The solution should be administered promptly after being made but is satisfactory for use for three hours after preparation.

If the patient is receiving a parenteral infusion, the Cytoxan solution may be injected into the rubber tubing if the solution is glucose or saline.

No thrombosis or thrombophlebitis has been reported from injections of Cytoxan. Extravasation of the drug into the subcutaneous tissues does not result in local reactions.

PRECAUTIONS: Cytoxan should not be given to any person with a severe leukopenia, thrombocytopenia, or bone marrow infiltrated with malignant cells. It may be given with suitable precautions to patients who have had recent x-ray treatment, recent treatment with a cytotoxic agent, a surgical procedure within 2-3 weeks, or debilitated patients.

AVAILABILITY: Cytoxan is available as follows:

Cytoxan for Injection, 100 mg., a sterile dry-filled vial containing 100 mg. cyclophosphamide and 45 mg. sodium chloride. Packaged, 12 vials per carton.

Cytoxan for Injection, 200 mg., a sterile dry-filled vial containing 200 mg. cyclophosphamide and 90 mg. sodium chloride. Packaged, 12 vials per carton.

Cytoxan Tablets for oral administration, 50 mg., white, round tablets, flecked with blue for easy identification. Packaged, 100 tablets per bottle.

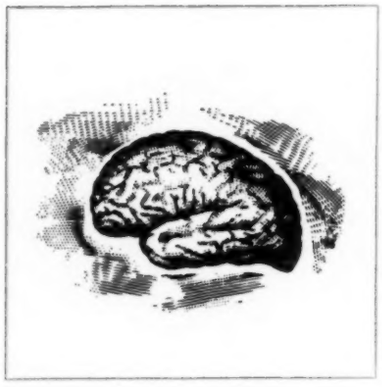
For a copy of the Cytoxan brochure, or other additional information on Cytoxan, communicate directly with the Medical Department, Mead Johnson Laboratories, Evansville 21, Indiana.

Mead Johnson
Laboratories

Symbol of service in medicine

52361

4 essential actions in one Rx: to bring most hypertensive patients under control

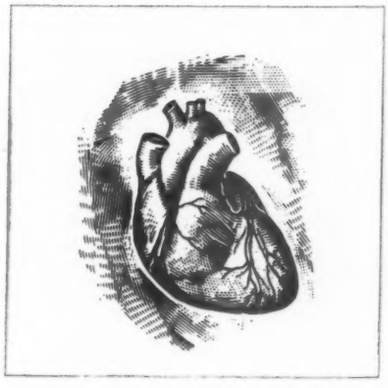


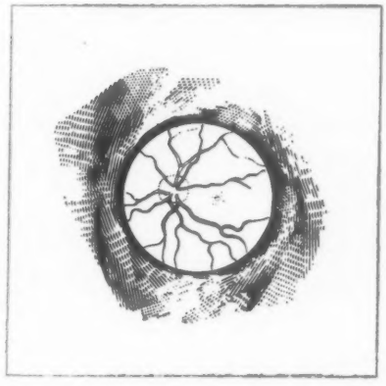
CENTRAL ACTION OF SER-AP-ES: SER-AP-ES acts centrally to inhibit or block the outflow of sympathetic vasopressor substances. In addition, Ser-Ap-Es improves cerebral vascular tone.

RENAL ACTION OF SER-AP-ES: Ser-Ap-Es increases renal blood flow, thereby halting or reversing the ischemic process in advancing hypertension. The increase in urine volume and sodium and chloride excretion which occurs with Ser-Ap-Es also benefits the hypertensive patient.

SERPASIL® (reserpine CIBA)
APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA)
ESIDRIX® (hydrochlorothiazide CIBA)

Most hypertensive patients need more than one drug, but most hypertensive patients need only one Rx ... Ser-Ap-Es®





CIBA
SUMMIT·NEW JERSEY

CARDIAC ACTION OF SER-AP-ES: Ser-Ap-Es has a beneficial effect on the hypertensive heart; diastole is prolonged, and there is a decrease in both heart rate and cardiac output—which combine to ease the strain on the overworked myocardium.

VASCULAR ACTION OF SER-AP-ES: Ser-Ap-Es opposes the action of pressor substances on the vasculature. In addition, Ser-Ap-Es makes the vasculature less responsive to circulating vasopressor amines and more responsive to the antipressor components of the combination tablet.

Supplied: SER-AP-ES *Tablets,* each containing 0.1 mg. Serpasil, 25 mg. Apresoline hydrochloride, and 15 mg. Esidrix. *For complete information about Ser-Ap-Es (including dosage, cautions, and side effects), see current Physicians' Desk Reference or write CIBA, Summit, N. J.*

Kills pain.....stops tension

For neuralgias, dysmenorrhea, upper respiratory distress, and postsurgical conditions—new compound of Soma, phenacetin and caffeine kills pain, stops tension, reduces fever—gives more complete relief than other analgesics . . . acts fast, relief lasts four to six hours

Composition: 200 mg. Soma (carisoprodol), 160 mg. phenacetin, 32 mg. caffeine. **Dosage:** 1 or 2 tablets q.i.d. **Supplied:** Bottles of 50 apricot-colored, scored tablets.

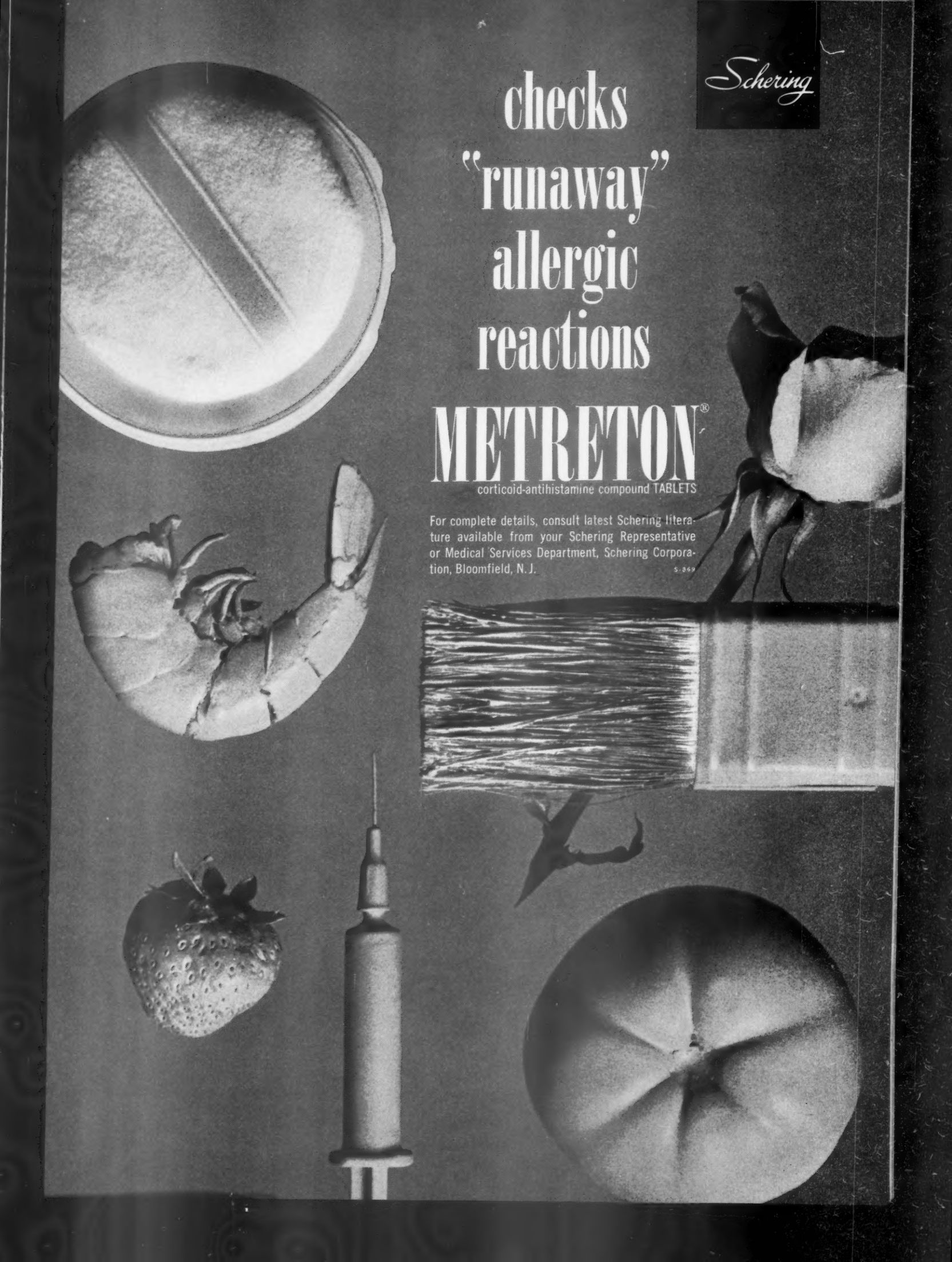
Also Available As
SOMA COMPOUND + CODEINE

Soma Compound boosts the effectiveness of codeine. SOMA COMPOUND + CODEINE therefore contains only ¼ grain of codeine phosphate to relieve the more severe pain that usually requires ½ grain. Otherwise, its composition—and dosage—is the same as Soma Compound. Supplied in bottles of 50 white, lozenge-shaped tablets.

soma® Compound

C80-5163

WALLACE LABORATORIES/Cranbury, N.J.


Schering
checks
"runaway"
allergic
reactions
METRETON®
corticoid-antihistamine compound TABLETS
For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, N.J.
S-869

The Clinical Study:[1]

38 patients, male and female, all of whom gained weight on a previous diet regimen.

The Rx:

Desoxyn Gradumet, 10 or 15 mg., *once daily*, in the morning.

The Clinical Result:

The entire group averaged a weight loss of 15 pounds between two and 12 months of treatment. Eight women, weighing between 178 and 269 pounds, took Desoxyn for six months. They averaged a loss of 34 pounds. The heaviest woman lost 57 pounds, while another lost 71 pounds.

All the results weren't good, of course. One male actually gained seven pounds after four months. And there were two other patients whose weight remained unchanged after four and six months of treatment.

A Sidelight:

The clinician noted that there was an occasional finding of tablets in stools. He wrote: "A certain doubt existed in our minds that this residual tablet did not contain amphetamine. We arranged

for analysis for four of such tablets in patients taking 15 mg. and found that in each instance, there was no trace of amphetamine."

The Conclusion:

"Desoxyn has the best patient acceptance of any of the medications we have used as an appetite suppressant . . . It is our impression that Desoxyn Gradumet does slowly release amphetamine and thus, reduce side effects that are a problem. It is likewise our impression that the medication is a definite aid in weight reduction and has a high patient acceptability. We are at present using this drug in our practice as a routine adjutant to a weight reduction program."

1. Cole, R. E., Communication to Medical Department, Abbott Laboratories, 1961

The Drug:

DESOXYN Gradumet®

(Methamphetamine Hydrochloride in Long-Release Dose Form*)

All-Day Appetite Control from a Single Oral Dose—5, 10 or 15 mg.

ABBOTT

*U.S. PAT. NO. 2,987,445 119242

Hostile Environment...

The fungus, protozoa and bacteria that commonly cause mild and severe leukorrhea require a vaginal pH of 5 to 12 for proliferation.

Trimagill creates a hostile environment! It produces a pH of 2.0 to 2.5—*the three principal infecting organisms cannot live in this acid range.*

Trimagill is well tolerated and has been proved effective in thousands of cases of leukorrhea, vaginitis, cervicitis, moniliasis and mixed infections. No untoward reactions that would require discontinuation of treatment were reported. At times denuded mucous membranes are so irritated that Trimagill may give a *temporary* burning sensation. This is usually short lived.

Trimagill does not foster resistant mutants or result in monilia overgrowth. Trimagill may be used during menstruation.

CONTENTS: Tartaric Acid, Citric Acid, Boric Acid, Dextrose, Potassium Alum, Potassium Bitartrate and Adhesives.

SUPPLIED: Powder: 5-oz. Plastic Insufflator Bottles; Vaginal Inserts: Boxes of 24.

NOTE: Consult package circular for information on dosage and instructions for use.

Write for descriptive literature.

TRIMAGILL®*

POWDER • VAGINAL INSERTS

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco

*Patent applied for.

new Renese®
POLYTHIAZIDE

1 mg. 2 mg. 4 mg.

A MORE CLINICALLY USEFUL
DIURETIC/ANTIHYPERTENSIVE

active antihypertensive
broad benefit
clinically confirmed
convenient control
dosage dexterity
dependable diuresis
enhanced effectiveness
foremost flexibility
increased individualization
long lasting
marked micturition
notable natruresis
orally optimal
peak potency
prolonged performance
reliable response
significant saluresis
tested toleration
unsurpassed utility
valuable versatility

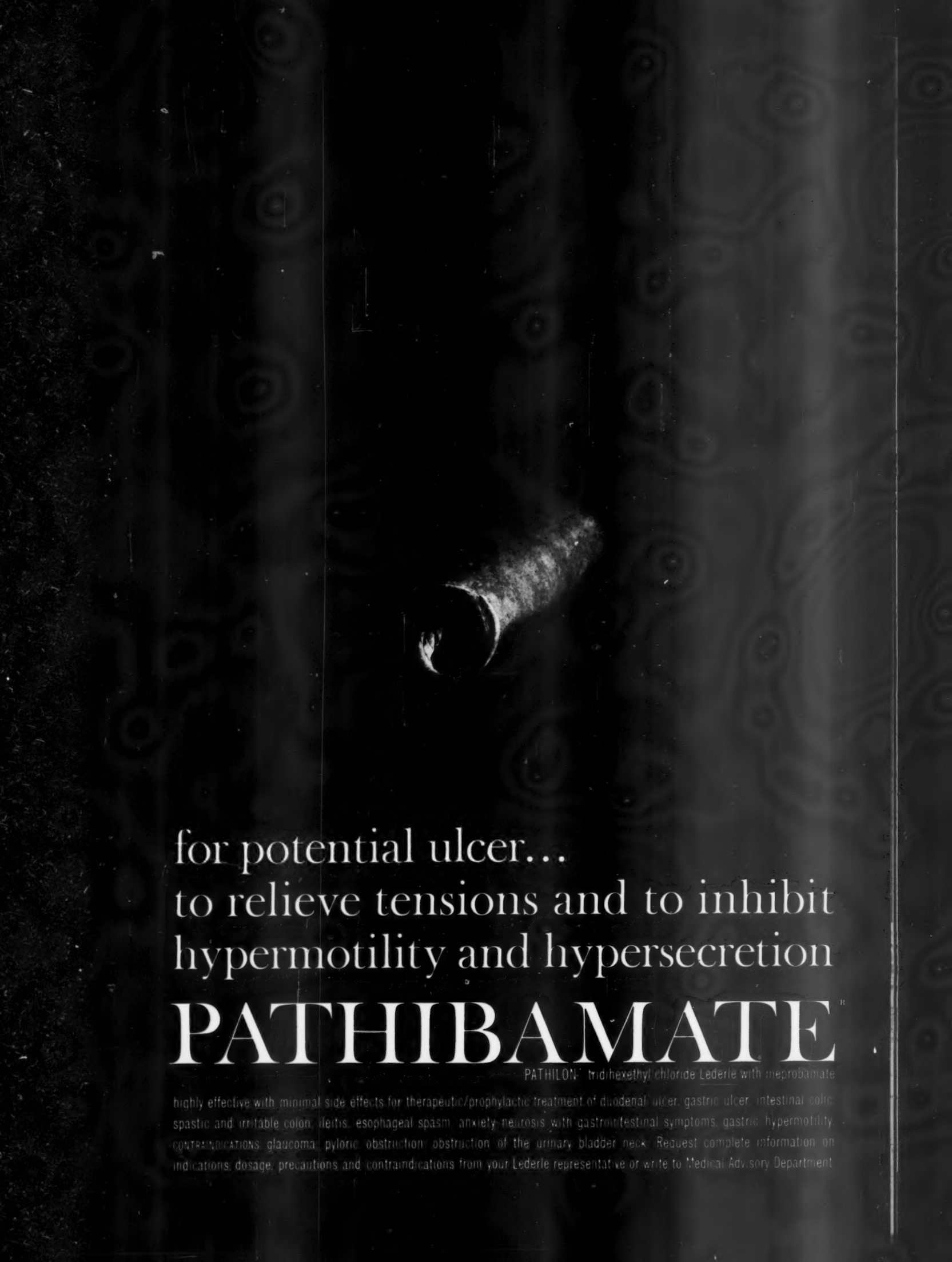
"prolonged performance" – RENESE activity lasts for at least 24 hours on a single dose[1]—thus assuring convenient once-a-day dosage for most patients, every-other-day dosage for selected patients. With RENESE available as 1 mg., 2 mg., and 4 mg. scored tablets, there is a once-a-day form for *each* and *every* patient – mild, moderate, or severe.

1. Ford, R. V.: Current Therap. Res. 3:320, July, 1961.

Pfizer *Science for the world's well-being®*

PFIZER LABORATORIES Division,
Chas. Pfizer & Co., Inc. New York 17, New York

FOR PRODUCT INFORMATION TURN TO PAGE 126

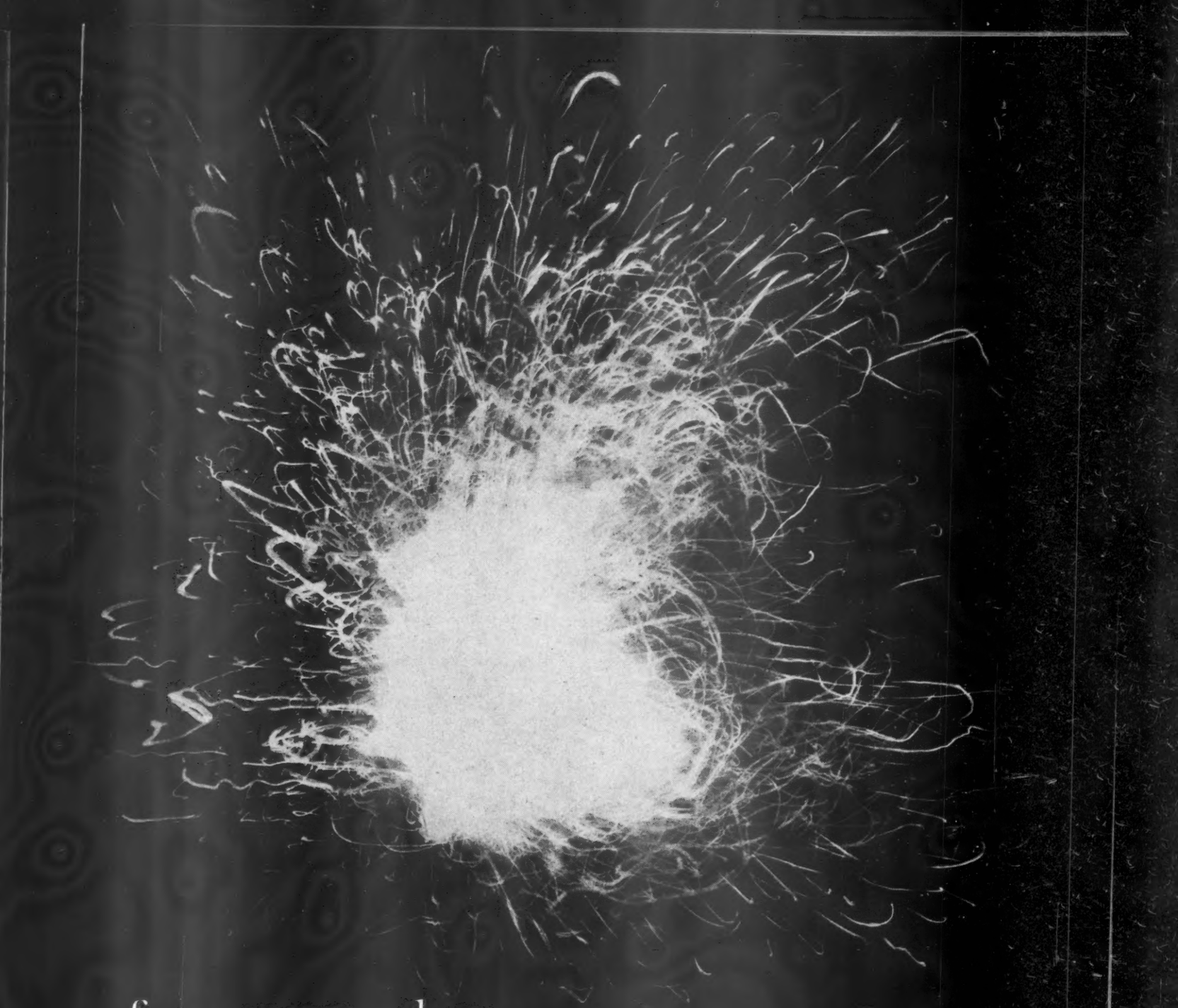


for potential ulcer...
to relieve tensions and to inhibit
hypermotility and hypersecretion

PATHIBAMATE®

PATHILON® tridihexethyl chloride Lederle with meprobamate

highly effective with minimal side effects for therapeutic/prophylactic treatment of duodenal ulcer, gastric ulcer, intestinal colic, spastic and irritable colon, ileitis, esophageal spasm, anxiety neurosis with gastrointestinal symptoms, gastric hypermotility. CONTRAINDICATIONS: glaucoma, pyloric obstruction, obstruction of the urinary bladder neck. Request complete information on indications, dosage, precautions and contraindications from your Lederle representative or write to Medical Advisory Department



for patent ulcer...
to relieve tensions and to inhibit
hypermotility and hypersecretion

PATHIBAMATE

PATHIBAMATE-400 (full meprobamate effect)—1 tablet t.i.d. at mealtime, and 2 tablets at bedtime · PATHIBAMATE-200 (limited meprobamate effect)—1 or 2 tablets t.i.d. at mealtime, and 2 tablets at bedtime · Adjust to patient response. Each Pathibamate-200 tablet contains: PATHILON, 25 mg.; meprobamate, 200 mg. Pathibamate-400 tablets contain 400 mg. meprobamate.

Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

BECAUSE POOR DIABETIC CONTROL INCREASES THE THREAT OF VASCULAR COMPLICATIONS IN DIABETES[1, 2]...
DIABINESE FIRST FOR ADEQUATE AND CONTINUOUS ORAL CONTROL

Oral therapy with DIABINESE can help assure more adequate blood-sugar control in many maturity-onset diabetics, including certain patients now poorly controlled by diet alone, some patients on insulin, and many who escape control on previous oral therapy.

Diabinese and diet

In patients with maturity-onset diabetes whose blood sugar remains elevated despite weight and/or caloric control, DIABINESE is frequently effective in doses of 100 to 250 mg. a day. Further, unlike insulin, DIABINESE has not been reported to increase appetite, and residual capacity for endogenous beta cell activity is stimulated. Thus, DIABINESE combined with dietary regulation will often ensure more satisfactory control than "diet alone."

Diabinese and the insulin patient

DIABINESE has proved to be an effective replacement for insulin among maturity-onset patients needing 40 units or less per day. This application of DIABINESE is especially valuable in patients who should not be exposed to the hazards and inconvenience of self-administered injection—those with poor eyesight, the infirm and elderly, and the emotionally disturbed. Transfer from insulin to DIABINESE in proper dosage lessens the risk of hypoglycemia, and may enable certain patients to resume occupations where insulin shock is considered dangerous.

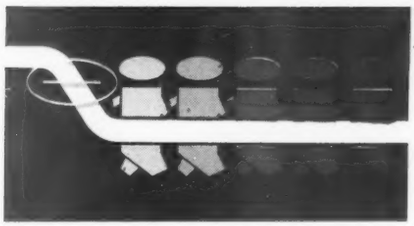
In selected patients in whom insulin requirements have become quite high, combined therapy with DIABINESE sometimes permits reduction of insulin dosage and helps to improve control.[3] Patients with insulin resistance may sometimes be similarly helped by replacement of part of the daily insulin dosage.[4]

Diabinese from the start

Continuous control in suitable candidates for sulfonylurea therapy is more likely to be achieved with DIABINESE. According to the A.M.A. Council on Drugs,[5] observations indicate that "on an equivalent dose and blood level basis, chlorpropamide has a somewhat greater therapeutic effect than has tolbutamide." This therapeutic superiority is reflected in the results of clinical observations like those of Fineberg,[6] who compared the effect of DIABINESE in 50 patients with the effect of tolbutamide in 35 patients. He concluded that "chlorpropamide produced satisfactory control of the diabetes in almost twice as great a percentage (76 versus 43 per cent) of patients than did tolbutamide, and excellent control in more than twice as great a percentage (74 versus 31 per cent)."

1. Johnsson, S.: Diabetes 9:1, 1960. 2. El Mahallawy, M. N., and Sabour, M. S.: J.A.M.A. 173:1783, 1960. 3. Editorial: Brit. M. J. 1:188, 1961. 4. Duncan, L. J. P., and Baird, J. D.: Pharmacol. Rev. 12:91, 1960. 5. A.M.A. Council on Drugs: New and Nonofficial Drugs, 1961, Philadelphia, Lippincott, 1961, p. 657. 6. Fineberg, S. K.: J. Am. Geriat. Soc. 8:441, 1960.

FOR MAXIMUM ASSURANCE OF CONTINUOUS BLOOD-SUGAR CONTROL



Diabinese®

BRAND OF CHLORPROPAMIDE

the oral antidiabetic most likely to succeed

economical once-a-day dosage

IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Like insulin, DIABINESE dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

SUPPLIED: As 100 mg. and 250 mg. scored chlorpropamide tablets.

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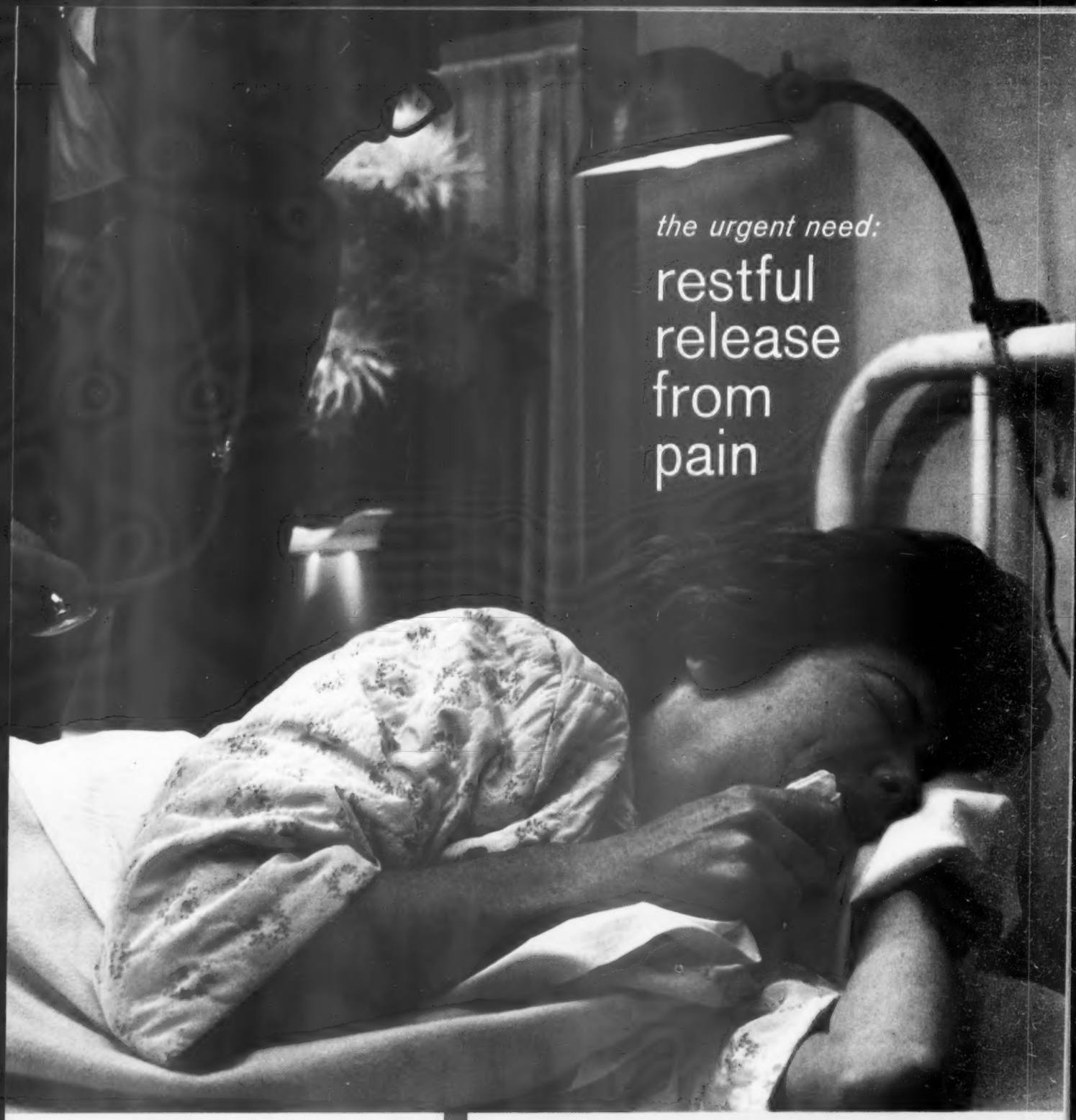

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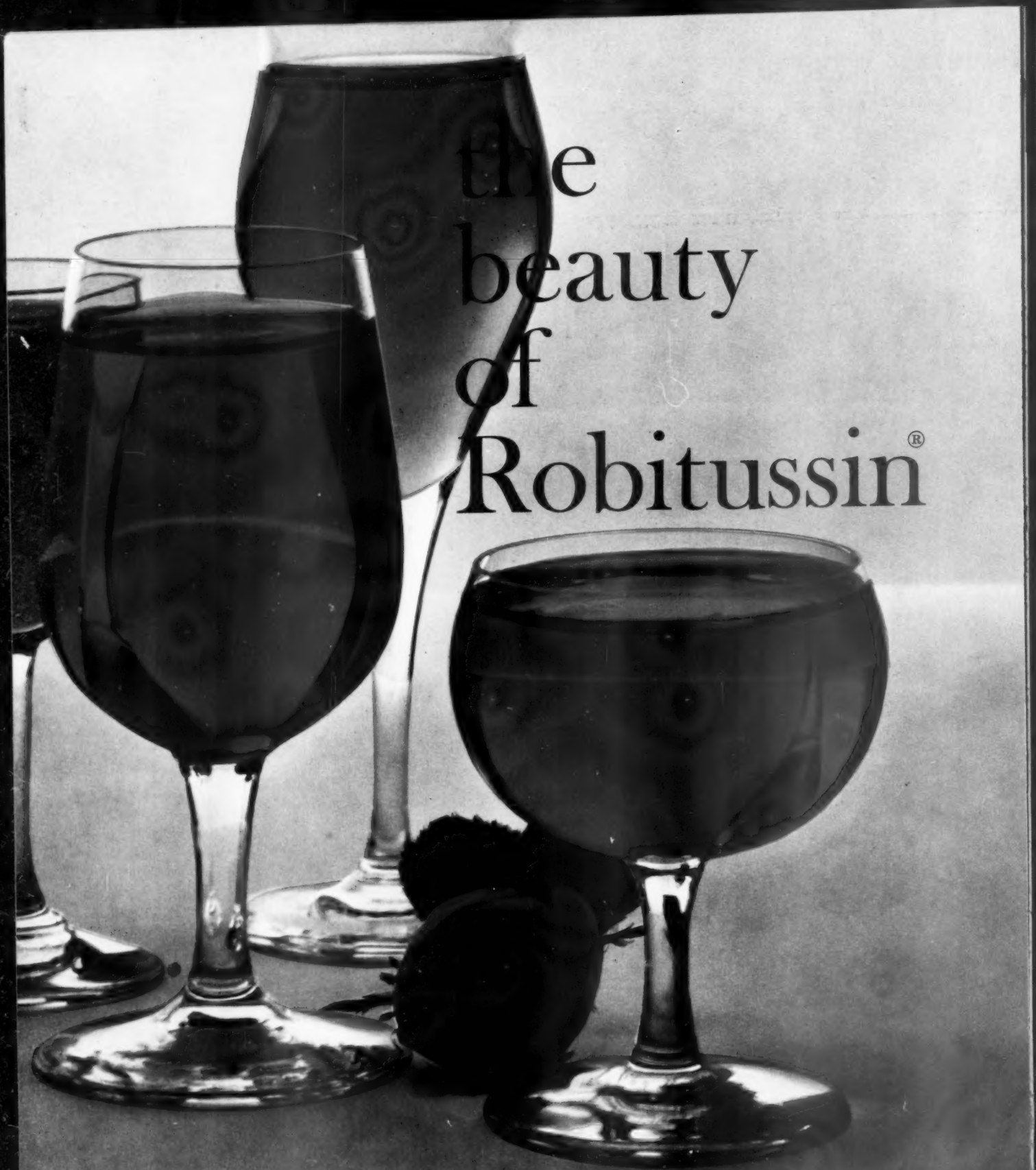

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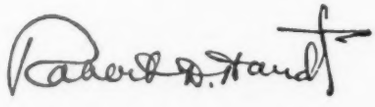

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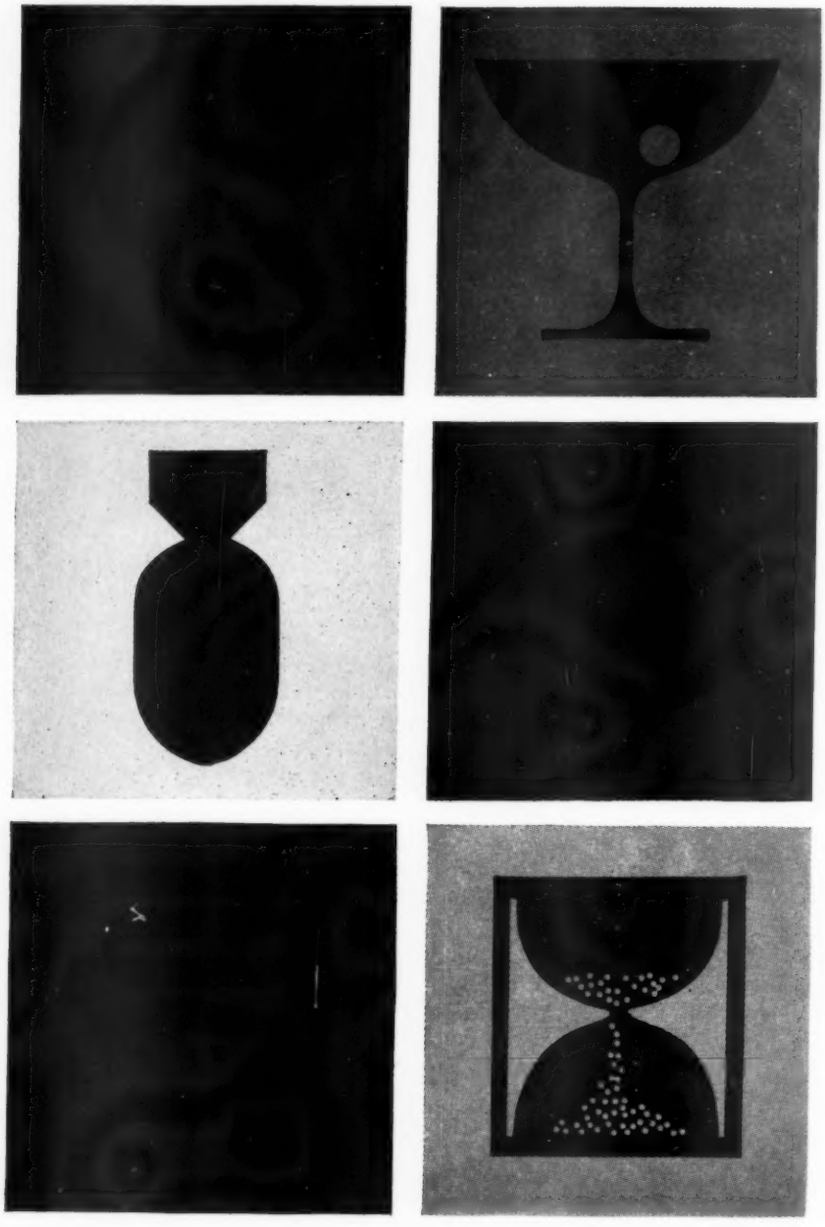

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maintains normal acuity Unlike many drugs, Listica does not affect unconditioned response or normal motor activity. Thus, Listica allays tension and anxiety without inducing apathy or impairing acuity; patients are able to pursue normal activities, such as driving, reading, writing, etc., without interference from drug therapy.

enhances physician-patient rapport As it removes tension/anxiety, fear and frustration, **LISTICA PROMOTES EUNOIA***—"a normal mental state." It bares the patient's true somatic condition, and facilitates diagnosis and therapy. Patients are more tractable to concomitant drug therapy, respond better, faster.

without known toxicity or contraindications Listica is safe, as well as effective. Chronic studies[14] in rats (12 months) and dogs (6 months) were free of toxic manifestations at oral dosage levels as high as 200 mg./kg./day (approximately 10 times the recommended human dosage). No macroscopic or microscopic changes in tissues, organs or blood indicative of toxicity were observed, even at doses up to 320 mg./kg. In humans, there have been no adverse blood, urine or cardiac changes; liver profiles were negative, and jaundice has not been noted.

without serious side effects or habituation During three and one-half years of clinical study in 1,759 patients,[2-13] Listica has produced no serious side effects. Less than 4% of patients experienced any side effects, and these were invariably minor and transient. Most frequent (38 cases) was mild drowsiness, which disappeared after the first few days of Listica therapy. Habituation, cumulative effects, or withdrawal symptoms have not been noted, even in patients taking Listica as long as two years.

with convenient dosage and availability One Listica tablet, q.i.d., is the recommended dosage. Listica is supplied in bottles of 50 tablets on prescription only, by pharmacies everywhere. Each tablet contains 200 mg. of Hydroxyphenamate, Armour.

References:

[1]Bastian, J. W.: Classification of CNS Drugs by a Mouse Screening Battery. To be published in Intern. Arch. de Pharmacodynamie; [2]Hubata, J. A., and Hecht, R. A.: Review of Clinical Use of Hydroxyphenamate (Listica) in 1,759 Patients. To be published in Clinical Medicine; [3]Taub, S. J.: Management of Anxiety in Allergic Disorders—New Approach. To be published in Psychosomatics; [4]Cahn, B.: Experience with a New Tranquilizing Agent (Hydroxyphenamate). *Ibid;* [5]Alexander, L.: Effect of Hydroxyphenamate on Conditional Psychogalvanic Reflex in Man. Supplement to Diseases of the Nervous System, Sept., 1961; [6]Cahn, B.: Effect of Hydroxyphenamate in Treatment of Mild and Moderate Anxiety States. *Ibid;* [7]Cahn, M. M., and Levy, E. J.: Use of Hydroxyphenamate (Listica) in Dermatological Therapy. *Ibid;* [8]Davis, O. F.: On Use of Hydroxyphenamate in Anxiety Associated with Somatic Disease. *Ibid;* [9]Eisenberg, B. C.: Amelioration of Allergic Symptoms with a New Tranquilizer Drug (Listica). *Ibid;* [10]Friedman, A. P.: Pharmacological Approach to Treatment of Headache. *Ibid;* [11]Greenspan, E. B.: Use of Hydroxyphenamate in Some Forms of Cardiovascular Disease. *Ibid;* [12]Lunde, F., Davis, J., and Gouldmann, C.: Clinical Trial of Hydroxyphenamate in Alcoholic Patients. *Ibid;* [13]McLaughlin, B. E., Harris, J., and Ryan, F.; Double Blind Study Involving "Listica," Chlordiazepoxide, and "Placebo" as Adjunct to Supportive Psychotherapy in Psychiatric Clinic. *Ibid;* [14]Bastian, J. W.: Pharmacology and Toxicology of Hydroxyphenamate. *Ibid;* [15]Bossinger, C. D.: Chemistry of Hydroxyphenamate. *Ibid.*

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If you were treating 25 pregnant, habitual aborters right now, what rate of success could you anticipate?

Lipp[1] administered DEPO-PROVERA to 25 pregnant, habitual aborters who totalled 94 previous successive abortions. Each patient had been under medical treatment for 8 to 48 months. DEPO-PROVERA was started between the third and eighth weeks of pregnancy. Six patients received an average of 5.7 injections of 25 mg. through the twentieth week, and 19 received an average of 4.4 injections of 50 mg. during the same period of time.

The results: The first group of 6 patients delivered 4 viable infants (67% salvage) while the second group of 19 patients delivered 16 (84% salvage). No side effects occurred and there was no evidence of female fetal masculinization.

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1. Lipp, R.G.: Habitual Abortion—Treatment with Parenteral Medroxyprogesterone Acetate, to be published.

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Brief Basic Information

	Description	Indications	Dosage: Threatened abortion	Dosage: Habitual abortion	Supplied	Precautions
Oral Provera*	Upjohn brand of medroxyprogesterone acetate.	Threatened and habitual abortion, infertility, secondary amenorrhea, functional uterine bleeding.	10 to 30 mg. daily until acute symptoms subside.	1st trim. 10 mg. daily 2nd trim. 20 mg. daily 3rd trim. 40 mg. daily, through 8th month.	2.5 mg. scored, pink tablets, bottles of 25; 10 mg scored white tablets, bottles of 25 and 100.	Clinically, Provera is well tolerated. No significant untoward effects have been reported. Animal studies show that Provera possesses adrenocorticoid-like activity. While such adrenocorticoid action has not been observed in human subjects, patients receiving large doses of Provera continuously for prolonged periods should be observed closely. Likewise, large doses of Provera have been found to produce some instances of female fetal masculinization in animals. Although this has not occurred in human beings, the possibility of such an effect, particularly with large doses over a long period of time, should be considered. Provera, administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated.
I. M. Depo-Provera*	Each cc. contains: Medroxyprogesterone acetate, 50mg., Polyethylene glycol 4000, 28.8 mg., Polysorbate 80, 1.92 mg.; Sodium chloride, 8.65 mg., Methylparaben, 1.73 mg., Propylparaben, 0.19 mg., Water for injection, q.s.	Threatened and habitual abortion.	50 mg. I.M. daily while symptoms are present, followed by 50 mg. weekly through 1st trimester or until fetal viability is evident.	1st trim. 50 mg. I.M. weekly 2nd trim. 100 mg. I.M. q. 2 wks. 3rd trim. 100 mg. I.M. q. 2 wks. through 8th month.	Sterile aqueous suspension for intramuscular use only, 50 mg. per cc., in 1 cc. and 5 cc. vials.	

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80%
fetal salvage
in 25
habitual
aborters
with
94 previous,
successive
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"The practicing physician translating this into his own needs may be completely confident of using a medication with an excellent predictability and a safe analgesic response."[1]

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INDICATIONS: Relief of pain in injury, low back pain, premenstrual cramping, dysmenorrhea, postoperative pain, and a wide variety of recurring and acute painful conditions.

DOSAGE: One capsule at onset of pain, followed by 1 capsule at intervals of 1 to 4 hours, as needed.

REFERENCES: From the Symposium, *Recent Concepts of Pain and Analgesia*, held in the Hall of States, American Hospital Association, Chicago, February 15, 1961: 1. Batterman, R. C.: *Non-Narcotic Analgesia in Ambulatory Patients.* 2. O'Dell, T. B.: *Experimental Parameters in the Evaluation of Analgesics.* 3. Miller, L. D.: *Distribution, Excretion and Metabolic Fate of Phenyramidol.* 4. Beisler, E.: *Preliminary Report of Experience with Phenyramidol for Dental Analgesia.* 5. Bader, G.: *Preliminary Report on the Use of Analexin for Dysmenorrhea in Telephone Operators.* 6. Taylor, S. L.: *Phenyramidol in General Hospital Orthopedics.* 7. Bodi, T.: *Pain Management Among Clinic Outpatients.* 8. Ramunis, J.: *Experience of an Industrial Surgeon with Phenyramidol.* 9. Kast, E. C.: *Methodological Considerations in the Clinical Evaluation of an Analgesic.* 10. Collopy, C. T.: *Preliminary Comparisons of Two Non-Narcotic Analgesic Agents in Hospitalized Orthopedic Patients.* 11. Cass, L. J.: *Report on the Analgesic and Calmative Effectiveness of Two Preparations on Patients with Acute and Chronic Pain.* 12. Lamphier, T. A.: *Intravenous Phenyramidol in the Management of Low Back Pain and Allied Disorders.* 13. O'Dell, T. B.: Chicago Med. *63*:9, 1961. 14. Kast, E. C.: Chicago Med. *63*:17, 1961. 15. Wainer, A. S.: J. Am. M. Women's A. *16*:218, 1961. 16. Batterman, R. C.: Ann. New York Acad. Sc. *86*:203, 1960. 17. O'Dell, T. B.: Ann. New York Acad. Sc. *86*:191, 1960. 18. O'Dell, T. B., *et al.*: J. Pharmacol. & Exper. Therap. *128*:65, 1960. 19. O'Dell, T. B., *et al.*: Fed. Proc. *18*:1694, 1959. 20. Gray, A. P., *et al.*: J. Am. Chem. Soc. *81*:4347, 1959. 21. Wainer, A. S.: Clin. Med. *7*:2331, 1960. 22. Clinical data in files of Medical Dept., Irwin, Neisler & Co., 1959. 23. Batterman, R. C., *et al.*: Am. J. Med. Sc. *238*:315, 1959.

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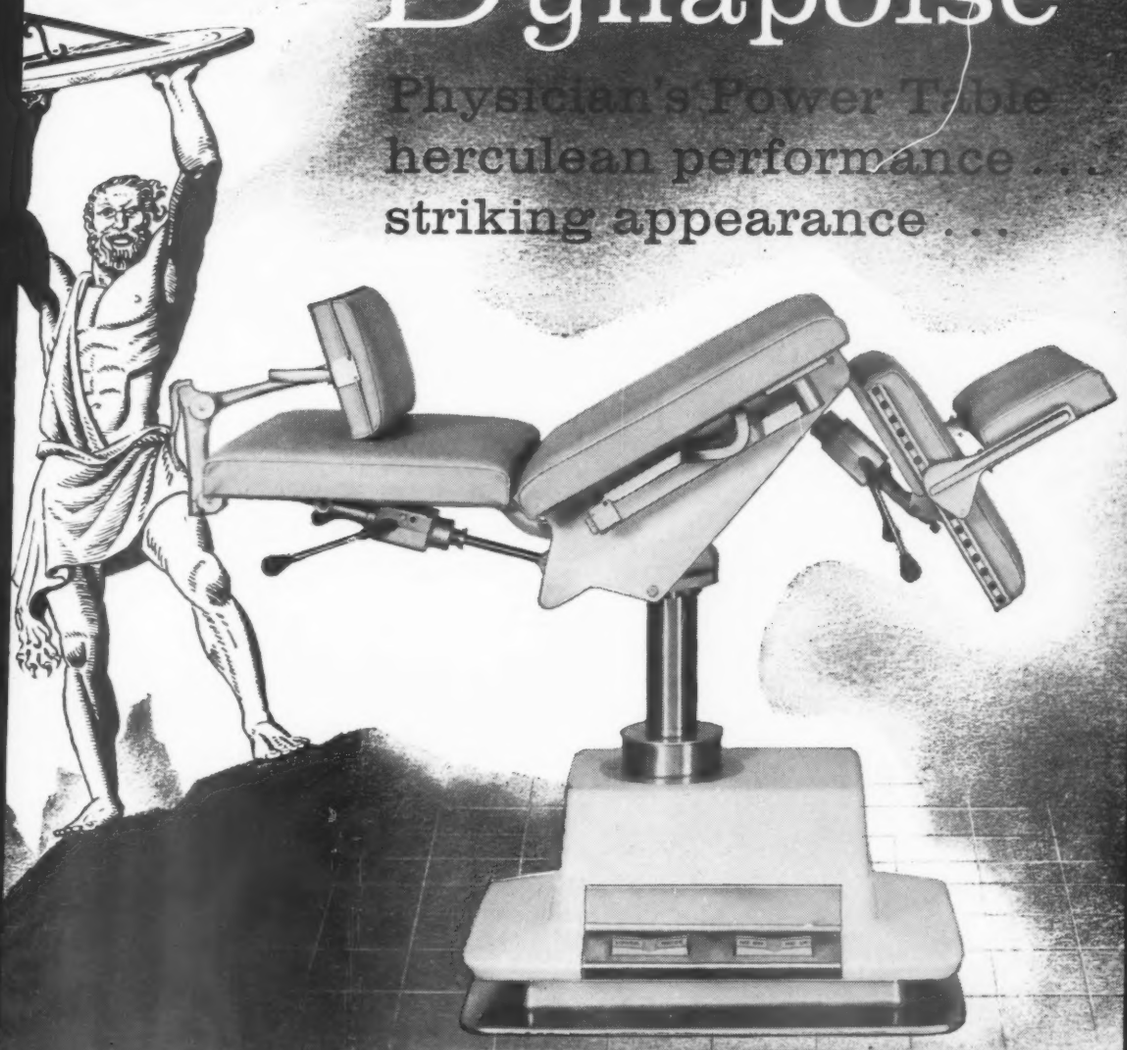

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Bibliography: 1. Cohen, A., et al.: J.A.M.A. 165: 225, 1957. **2.** Spies, T. D., et al.: J.A.M.A. 159: 645, 1955. **3** Moravec, C. L. and Moravec, M. E.: Clin. Med. 7:2322, 1960.

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Counters fatigue naturally . . . with high order of safety

SPARTASE provides *natural, physiologic* treatment for fatigued patients. It may be used either alone in functional disorders or, adjunctively, in the presence of organic disease.

Not a CNS stimulant, enzymatic inhibitor or antidepressant.

In selected cases, SPARTASE restores normal work capacity.

OFFICIAL BROCHURE

SPARTASE is a mixture of equal amounts of the potassium and magnesium salts of aspartic acid. Pharmacological and clinical observations have been made which indicate that SPARTASE participates in intermediary metabolism in such a fashion as to be effective therapeutically in the management of fatigue.

General Pharmacological Properties—The IP and PO LD_{50} values for SPARTASE in rats are 4 and 19 grams/kg., respectively.

The pharmacological activity of aspartic acid has been the subject of numerous publications[1-8] and need not be reviewed.

Laborit *et al.*[9,10] studied the effects of the combined K and Mg aspartates on groups of white rats subjected to the standard swim test. It was found that duration of swim after this therapy was significantly prolonged over that achieved with other regimens attempted. After a standard rest period of 2½ hours, the aspartate-treated animals again swam longer than any other group.

Plasma ammonia levels were measured in groups of rats similarly exposed to swim effort and drug therapy. Increase in ammonia levels noted in the controls[11] was not seen in the group pretreated with the aspartates.

A group of 16 dogs breathing a mixture of 90% oxygen and 10% CO_2 was given the combined salts of aspartic acid parenterally. Plasma and expired CO_2 tension decreased, and plasma urea concentration increased immediately[12].

The administration of K and Mg aspartates to athletes demonstrated a positive effect on neuro-muscular irritability, a significant reduction in existing fatigue and a significant prophylactic effect against the induction of fatigue[10,13,14].

Indications—The use of SPARTASE for the treatment of fatigue is not intended to supplant specific treatment for accompanying organic disease or to substitute for specific indications for potassium.

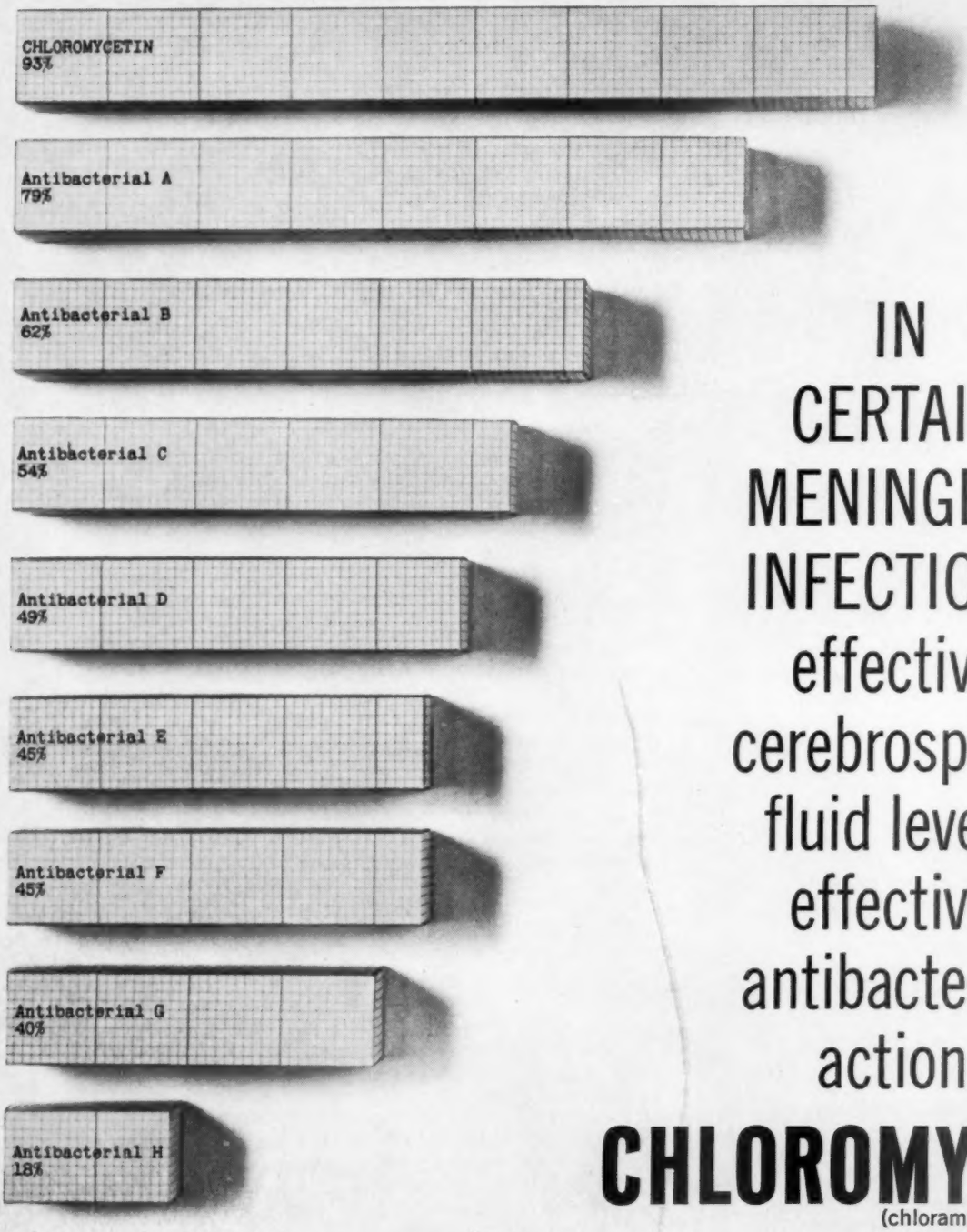
SPARTASE has a wide range of clinical utility in the management of the fatigue syndrome. It may be used effectively in the management of many fatigue problems, whether or not associated with functional or organic disease. SPARTASE is particularly useful in treating the tired patient with no evidence of organic dysfunction.

Dosage and Administration—The adult dose of SPARTASE is two 500 mg. tablets after the morning and evening meals. Approximately four days therapy are required before subjective clinical improvement may be noted; it is suggested that SPARTASE administration be continued for at least two weeks before the patient is re-evaluated.

Contraindications and Side Effects—Nausea, abdominal discomfort and diarrhea have been noted occasionally. These symptoms may be minimized by proper administration of dose after meals.

There are no known contraindications to SPARTASE therapy.

References—1. H. Kamin, P. Handler: J. Biol. Chem. *193*:873-80 (1951). 2. H. Resnik, M.F. Mason: Am. J. Med. Sci. *192*:520-5 (1936). 3. J.A. Brockman, Jr., S.L. Burson, Jr.: Proc. Soc. Exptl. Biol. Med. *94*:450-2 (1957). 4. H.H. Tallan: J. Biol. Chem. *224*:41-5 (1957). 5. B.J. Miller, V.W. Ciacci, S.P. Reimann: Growth *5*:329-50 (1941). 6. S. Edlbacher, K. Schmid: Helv. Chim. Acta *28*: 1079-88 (1945). 7. D.P. Tschudy, M. Marshall, A. Graff, S. Graff: Cancer *11*:984-95 (1958). 8. M.N. Mickelson, R.S. Flippin: Arch. Biochem. Biophys. *64*:246-8 (1956). 9. H. Laborit, R. Moynier, A. Trzebski, G. Guiot, C. Baron: Compt. rend. soc. biol. *151*:1383-6 (1957). 10. C. Vial: Imprimerie des Tournelles, Paris, 1959. 11. H. Laborit, L. Obrenovitch, P. LeGuen: Compt. rend. soc. biol. *152*:1359-60 (1958). 12. H. Laborit, P. Niaussat, J.M. Jouany, B. Weber, J. Martin, C. Baron: Compt. rend. soc. biol. *152*:1094-7 (1958). 13. Thiebault: Bull. mens. soc. med. mil. franc. *52*:139-49 (1958). 14. H. Laborit, B. Weber, P. Niaussat, J.M. Jouany, G. Guiot, J. Zawadowski, C. Baron: Anesthésie et analgésie *15*:480-94 (1958).



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Sensitivity tests were done by the disc method on a total of 100 strains of *H. influenzae* obtained on clinical isolates from 1955 through 1958.

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Warning: Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, or viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

B4161

PARKE-DAVIS

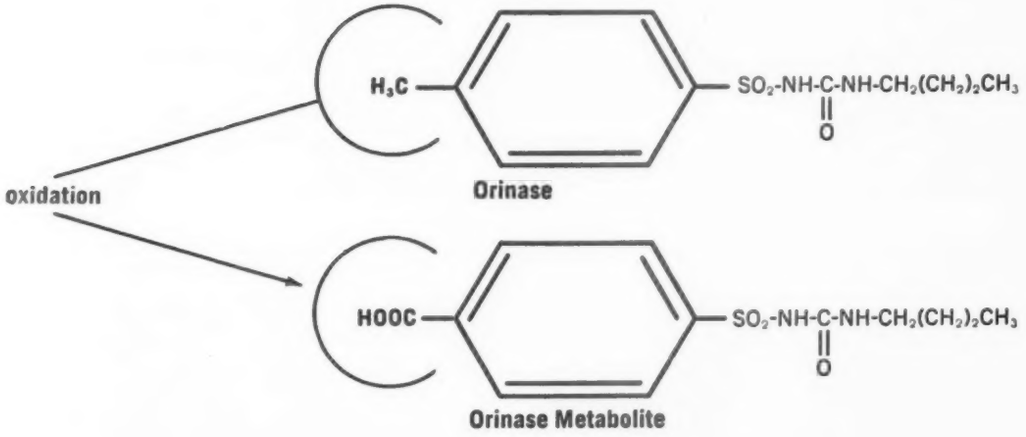
PARKE, DAVIS & COMPANY, Detroit 32, Michigan

Why is the methyl "governor" in Orinase so important?

One of the most significant advantages of Orinase therapy is the rarity of associated hypoglycemic reactions.

This widely-reported clinical benefit is a function of the exclusive Orinase methyl "governor." Lending itself to ready oxidation (principally, it is thought, a hepatic process), the methyl group ensures prompt metabolic inactivation of the Orinase molecule. What actually happens is that a rapidly- and continuously-excreted carboxy-metabolite is produced that has no hypoglycemic activity at the existing levels.

As a result of the oxidation of its methyl group, Orinase shows a decline in activity soon after it reaches its effective peak in the plasma. Maintenance dosage serves to reduce blood sugar levels to normal, but rarely below that point, and there is no reported problem of accumulation.



Orinase*

An exclusive methyl "governor" minimizes hypoglycemia

Indications and effects: The clinical indication for Orinase is stable diabetes mellitus. Its use brings about the lowering of blood sugar; glycosuria diminishes, and such symptoms as pruritus, polyuria, and polyphagia disappear.

Dosage: There is no fixed regimen for initiating Orinase therapy. A simple and effective method is as follows: *First day*—6 tablets; *second day*—4 tablets; *third day*—2 tablets. The daily dose is then adjusted—raised, lowered or maintained at the two-tablet level, whichever is necessary to maintain optimum control.

Patients receiving insulin (less than 20 units)—discontinue insulin and institute Orinase; (20 to 40 units)—initiate Orinase with a concurrent 30 to 50% reduction in insulin dose with a further careful reduction as response to Orinase is observed; (more than 40 units)—reduce insulin by 20% and initiate Orinase with a further careful reduction in insulin dosage as response to Orinase is observed. In candidates for combined Orinase-insulin therapy, an individualized schedule is usually obtainable during a trial course of two or more weeks.

Contraindications and side effects: Orinase is contraindicated in patients having juvenile or growth-onset, unstable or brittle types of diabetes mellitus; history of diabetic coma, fever, severe trauma or gangrene.

Side effects are mild, transient and limited to approximately 3-4% of patients. Hypoglycemia and toxic reactions are extremely rare. Hypoglycemia is most likely to occur during the period of transition from insulin to Orinase. Other untoward reactions to Orinase are usually not of a serious nature and consist principally of gastrointestinal disturbances, headache, and variable allergic skin manifestations. The gastrointestinal disturbances (nausea, epigastric fullness, heartburn) and headache appear to be related to the size of the dose, and they frequently disappear when dosage is reduced to maintenance levels or the total daily dose is administered in divided portions after meals. The allergic skin manifestations (pruritus, erythema, and urticarial, morbilliform, or maculopapular eruptions) are transient reactions, which frequently disappear with continued drug administration. However, if the skin reactions persist, Orinase should be discontinued.

Clinical toxicity: Orinase appears to be remarkably free from gross clinical toxicity on the basis of experience accumulated during more than four years of clinical use. Crystalluria or other untoward effects on renal function have not been observed. Long-term studies of hepatic function in humans and experience in over 650,000 diabetics have shown Orinase to be remarkably free of hepatic toxicity. There has been reported only one case of cholestatic jaundice related to Orinase administration, which occurred in a patient with pre-existing liver disease and which rapidly reversed upon discontinuance of the drug.

Each tablet contains:
Tolbutamide ..... 0.5 Gm.

Supplied: In bottles of 50.

*Trademark, Reg. U.S. Pat. Off.—tolbutamide, Upjohn

June, 1961

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The Upjohn Company, Kalamazoo, Michigan

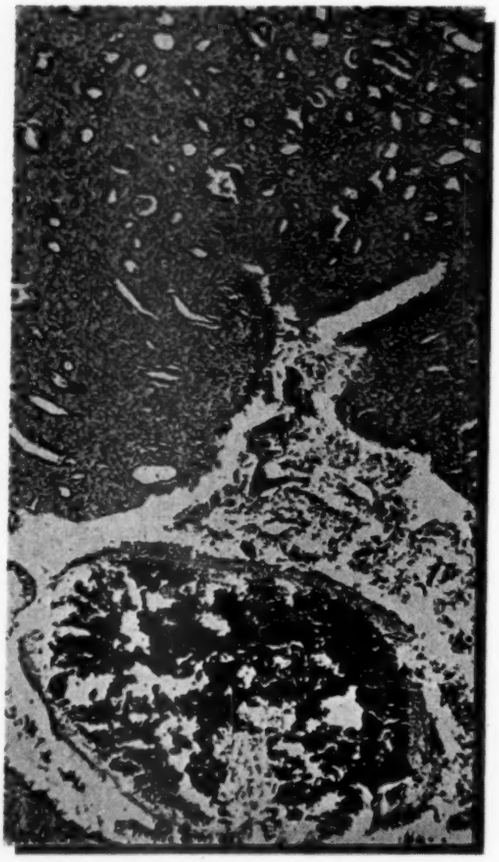
Upjohn

GOUT

"For centuries the victims of gout have been the subject of lampoons and caricatures. We now know that they should rather be the objects of great concern, for the disease is painful, disabling and is accompanied by complications that impair health and shorten life."[1]

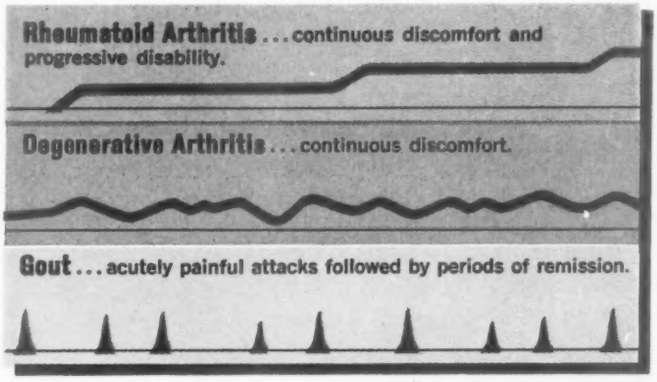
Kidney impairment, with varying degrees of hypertension and arteriosclerosis, is the critical complication of gout. "From 30 to 50 per cent of gouty patients are said to die of renal disease."[2]

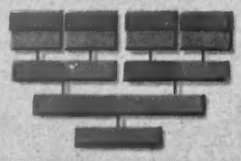
Tophus in the calyx, surrounded by fibrinoid exudate and detached mucosal epithelium.[3]



The mid- and outer portion of the pyramid with typical uric acid crystals in the collecting system.[3]

AIDS TO DIAGNOSIS


Rheumatoid Arthritis . . . continuous discomfort and progressive disability.
Degenerative Arthritis . . . continuous discomfort.
Gout . . . acutely painful attacks followed by periods of remission.



"If a family history of gout is obtained, even though it is one or two generations removed, this information is significant."[4]

"The metatarsophalangeal joint of a great toe is affected early or repeatedly in some cases, rarely or never in others."[6]

"All patients complaining of non-traumatic musculoskeletal discomfort should have at least one serum uric acid determination."[5]

Colchicine test: "Colchicine should be administered as early as possible after the onset of articular distress, 1 mg. . . . every 2 hours until the onset of gastro-intestinal distress. From 5 to 8 mg. usually are required."[9] Pain relief is highly indicative of gout.

THE "INSULIN OF GOUT"[7]

"Of the various drugs with uricosuric activity, probenecid [BENEMID] has proved most desirable for long-term administration."[8]

BENEMID®

PROBENECID

Therapy with BENEMID should be continued without interruption since hyperuricemia recurs when dosage is terminated. The rare patient who experiences gastric discomfort is usually benefited by decreasing the dosage. Dosage: 0.25 Gm. twice daily for one week, followed by 1 Gm. daily in divided doses. Supply: 0.5 Gm. tablets.

A COMPLEMENTARY FORMULATION OF TWO CLASSIC ANTI-GOUT AGENTS

"... the greater the experience we have with the combination of colchicine and Benemid the greater the reliance we place upon these two drugs."[9]

ColBENEMID®

COLCHICINE WITH BENEMID

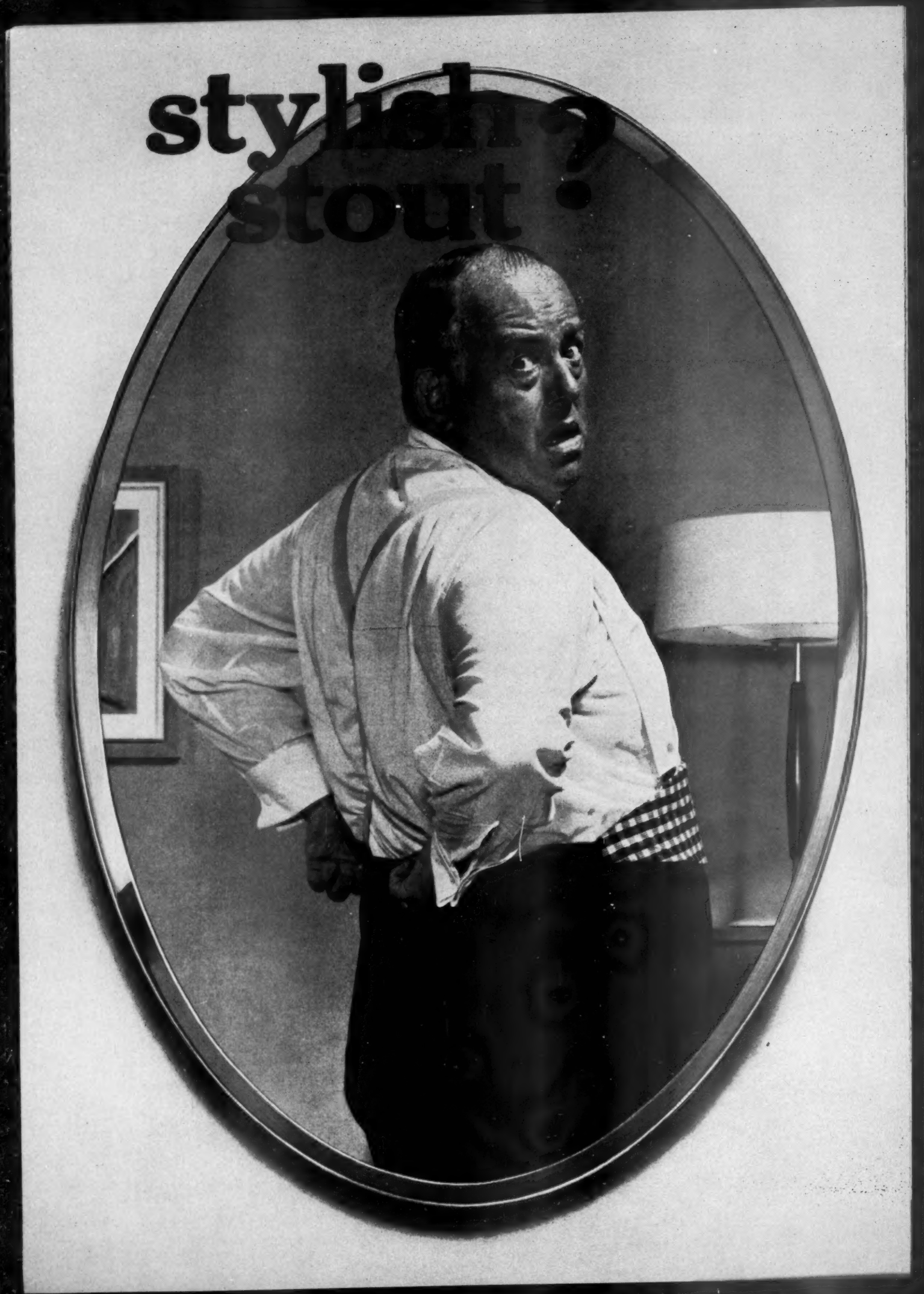
Dosage: One tablet daily for one week, followed by one tablet twice daily. Supply: Each tablet contains 0.5 mg. colchicine and 0.5 Gm. BENEMID. Bottles of 100 and 1000.

1. Cornish, A. L.: J. Kentucky M.A. 58:707, June, 1960. 2. Wyngaarden, J. B.: Arthritis & Rheumatism 1:191, June, 1958. 3. Talbott, J. H. and Terplan, K. L.: Medicine 39:405, Dec., 1960. 4. Talbott, J. H.: Gout, New York, Grune & Stratton, 1957, p. 123. 5. Kuzell, W. C., et al.: J. Chron. Dis. 2:645, Nov., 1955. 6. Hench, P. S.: Gout and gouty arthritis, in Cecil, R. L.: A textbook of medicine, ed. 10, Phila., W. B. Saunders Co., 1959. 7. Bartels, E. C., and Kepkay, P. H.: Bull. Vancouver M.A. 29:306, April, 1953. 8. Boland, E. W.: World-Wide Abstracts of Gen. Med. 3:16, Jan., 1960. 9. Talbott, J. H.: Current Med. Dig. 26:57, Nov., 1959.

Before prescribing or administering BENEMID or ColBENEMID, the physician should consult the detailed information on use accompanying the package or available on request.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

BENEMID AND COLBENEMID ARE TRADEMARKS OF MERCK AND CO., INC.


stylish?
stout?

UNDER YOUR SUPERVISION

Obedrin®

and the 60-10-70 menu plan can help patients bring weight down and as your judgment dictates... keep weight down!

This logical Obedrin formula helps bring weight down by helping control abnormal food cravings:

- Semoxydrine HCl (Methamphetamine) . . . 5 mg.—proved anorexigenic and mood-lifting effects
- Pentobarbital . . . 20 mg.—guards against excitation
- Ascorbic Acid . . . 100 mg.—aid for mobilization of tissue fluids
- Thiamine Mononitrate . . . 0.5 mg. } effective
- Riboflavin . . . 1 mg. } diet
- Nicotinic Acid (Niacin) . . . 5 mg. } supplementation

The 60-10-70 Menu Plan helps correct unhealthy eating habits without calorie counting—assures balanced food intake.

Supplied: Tablets and Capsules—bottles of 100, 500 and 1000.

WRITE FOR 60-10-70 MENU PLANS, WEIGHT CHARTS AND SAMPLES OF OBEDRIN.

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco

Remarkably useful in a wide variety of inflammatory conditions, including: rheumatoid arthritis, spondylitis, osteoarthritis[1-6]; gout,[1,7,8]; acute superficial thrombophlebitis[9,10]; painful shoulder (peritendinitis, capsulitis, bursitis, and acute arthritis of that joint)[1,7]; severe forms of a variety of local inflammatory conditions.[11,12,13]

The physician should be thoroughly familiar with the dosage, side effects, precautions and contraindications of Tandearil before prescribing.

Full product information available on request.

more specific than steroids—Acts directly on the inflammatory lesion without altering pituitary-adrenal function...without impairing immunity responses.[11,14]

more dependably absorbed than enzymes—Tandearil, a simple, non-protein molecule, is rapidly and completely absorbed,[4,16] consistently providing effective blood levels.

far more potent than salicylates—Anti-inflammatory potency of Tandearil markedly superior to aspirin.[2,15]

availability:
Round, tan, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York

references:
1. Graham, W.: Canad. M. A. J. **82**:1005 (May 14) 1960. 2. Vaughn, P. P.; Howell, D. S., and Kiem, I. M.: Arth. and Rheumat. **2**:212, 1959. 3. O'Reilly, T. J.: J. Irish M. A. **46**:106, 1960. 4. Cardoe, N.: Ann. Rheumat. Dis. **18**:244, 1959. 5. Robichaux, E.: General Practice **24**:14, 1961. 6. Brooke, J. W.: Western Med. **2**:81, 1961. 7. Connell, J. F., Jr., and Rousselot, L. M.: Am. J. Surg. **98**:31, 1959. 8. Brodie, B. B., et al., in Contemporary Rheumatology 1956, p. 600. 9. Stein, I. D.: Ann. N. Y. Acad. Sc. **86**:307 (March 30) 1960. 10. Barczyk, W., and Röth, W.: Praxis **49**:589, 1960. 11. Miller, J. M., et al.: Antibiotic Med. and Clin. Therap. **7**:109, 1960. 12. Connell, J. F., Jr., and Rousselot, L. M.: Am. J. Surg. **97**:429, 1959. 13. Summary of individual case histories submitted to Geigy. 14. Domenjoz, R.: Ann. N. Y. Acad. Sc. **86**:263, 1960. 15. Smyth, C. J.: Ann. N. Y. Acad. Sc. **86**:292, 1960. 16. Yü, T. F., et al.: J. Pharmacol. and Exper. Therap. **123**:63, 1958.

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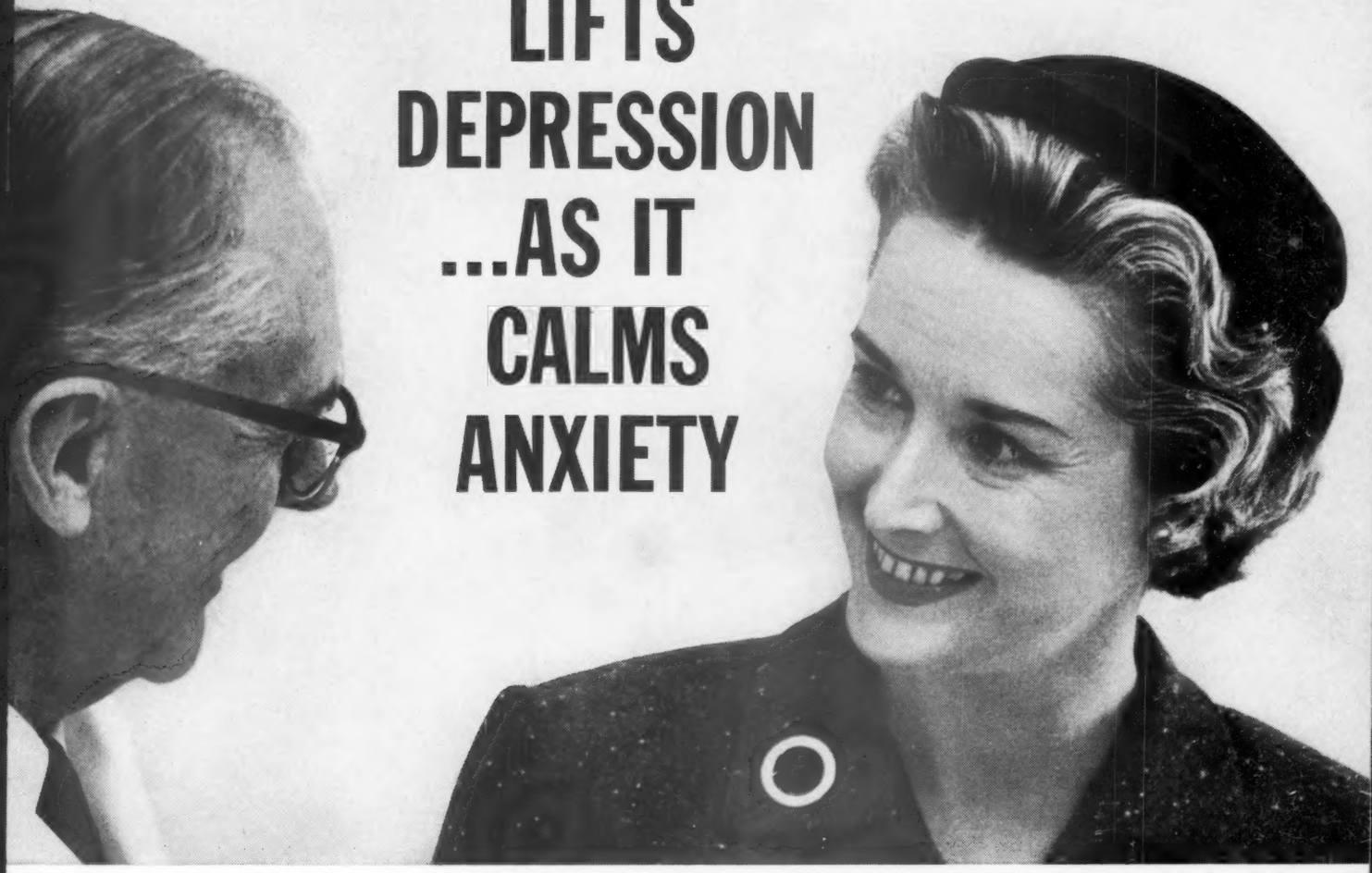
LIFTS DEPRESSION ...AS IT CALMS ANXIETY



"I feel like my old self again!" Thanks to your balanced Deprol therapy, normal drive and interest have replaced her emotional fatigue.

Brightens up the mood, brings down tension

Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines. While energizers and amphetamines may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression and emotional fatigue.*

These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety – a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

Acts rapidly – you see improvement in a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – *often within a few days.* Thus, the expense to the patient of long-term drug therapy can be avoided.

Compatible with therapy for physical diseases. Deprol can be used safely with specific therapies for cardiovascular, G.I. and upper respiratory conditions. It does not cause liver damage, hypotension or tachycardia.

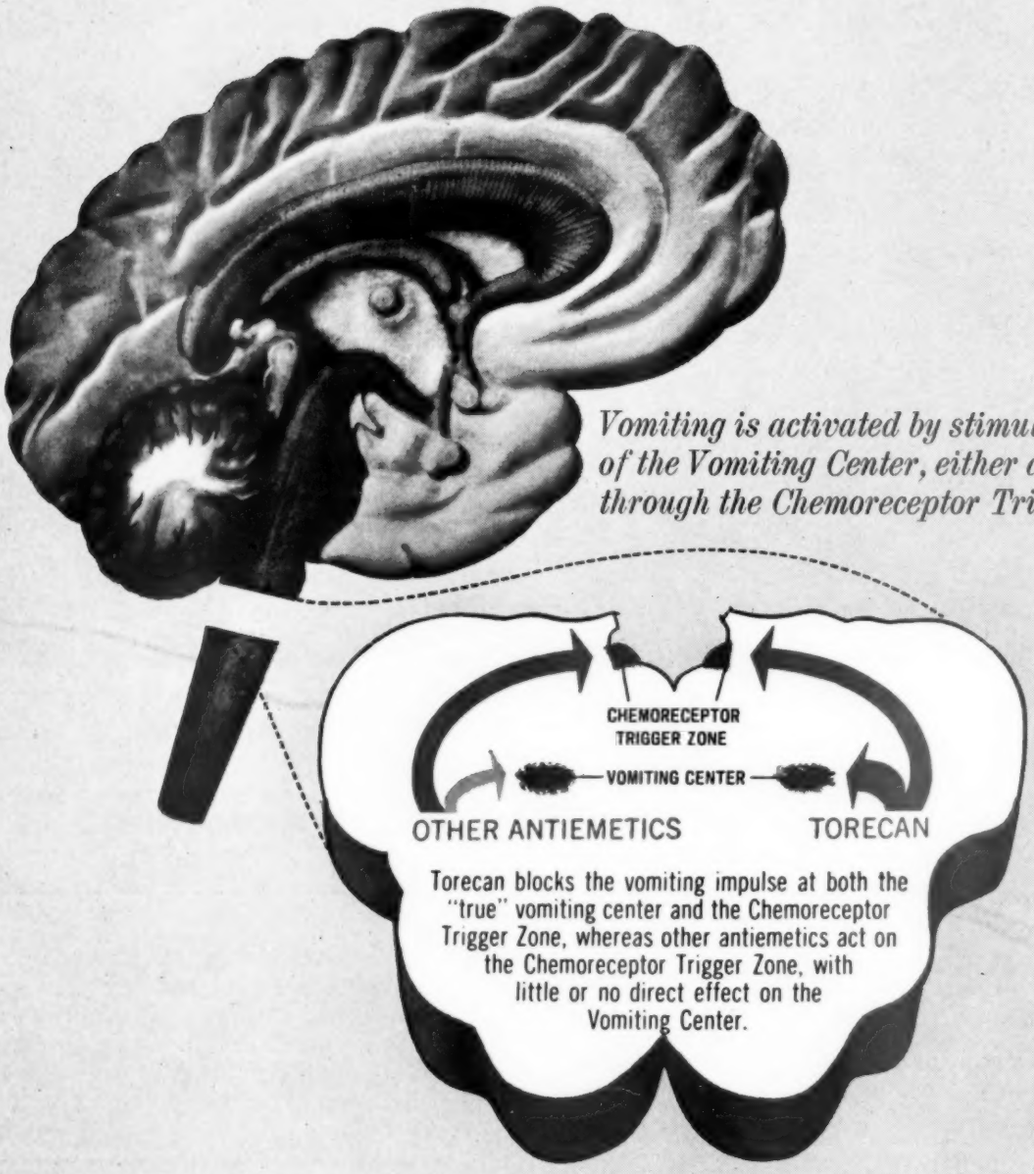
▲Deprol▲®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

WALLACE LABORATORIES / *Cranbury, N.J.*

CD-5619

Announcing...a "broadening of the antiemetic spectrum of effectiveness"[1]


CHEMORECEPTOR
TRIGGER ZONE
VOMITING CENTER
OTHER ANTIEMETICS
TORECAN
Torecan blocks the vomiting impulse at both the "true" vomiting center and the Chemoreceptor Trigger Zone, whereas other antiemetics act on the Chemoreceptor Trigger Zone, with little or no direct effect on the Vomiting Center.

Vomiting is activated by stimulation of the Vomiting Center, either directly or through the Chemoreceptor Trigger Zone.

"Thiethylperazine dimaleate [TORECAN] inhibits apomorphine vomiting [apomorphine elicits vomiting solely through the Chemoreceptor Trigger Zone[2,3,4]] in an even more pronounced manner than the well-known strong antiemetic, prochlorperazine. Thiethylperazine dimaleate also antagonizes oral copper sulfate [copper sulfate may activate the Vomiting Center directly or may act via the Chemoreceptor Trigger Zone]. Interestingly, only slightly higher dosages are needed for this than for the inhibition of apomorphine vomiting, whereas far higher dosages are required of other phenothiazines. This peculiarity of thiethylperazine of influencing not only the trigger zone, but also the vomiting center is of much therapeutic interest because of the broadening of the antiemetic spectrum of effectiveness."[1]

"When evaluating new antiemetic agents, it is necessary to pay close attention to the associated effects on the central and autonomic nervous systems. The aim is to find agents which will specifically depress the emetic mechanism with minimal effects elsewhere."[8]

TORECAN

provides specific antiemetic action with minimal "spillover" effects:

Tranquilizing or sedative action	Insignificant
Potentiation of sedative and anesthetic drugs	Only slight potentiation; less than with other phenothiazine antiemetics
Extrapyramidal symptoms, such as motor restlessness, muscular rigidity, parkinsonism, etc.	Rarely at dosage levels of 30-50 mg. per day
Cardiovascular effects (hypotension, cardiac acceleration)	Rare; less than with other phenothiazine antiemetics
Liver, blood, or renal toxicity	None reported
Other side effects: dizziness, dry mouth, weakness, fatigue, blurring of vision, headache, insomnia, constipation or diarrhea	Rare

"an extremely effective antiemetic in a large number of clinical conditions"[5]

Nausea and Vomiting of Pregnancy[6]

Nausea and Vomiting Associated with Gastroenteritis and Colitis[5,6,7]

Nausea and Vomiting due to Radiation and Nitrogen Mustard Therapy[1]

Postoperative Nausea and Vomiting[5]

Nausea and Vomiting Associated with Miscellaneous Non-inflammatory Conditions[5,6,7]

Nausea and Vomiting Associated with Labyrinthine Disturbances

Adult Dosage: Oral: 1 tablet 3 times daily
Intramuscular: 10 – 20 mg. daily

Supply: Tablets, 10 mg.; Ampuls, 2 cc. (10 mg.), each cc. contains 5 mg.

Precautions: It is obvious that, before using an antiemetic, clinical judgment must be exercised in determining whether vomiting represents a warning of organic abnormality and that this must first be recognized before employing a potent antiemetic such as TORECAN. Drowsiness and/or dryness of the mouth may occur with doses above 30 mg. daily. While no hepatic, hematopoietic or renal toxicity have been reported at recommended dosage levels, it should be remembered that these reactions may occur with phenothiazines. Orthostatic hypotension may be manifested at higher dose levels. TORECAN is contraindicated in severely depressed or comatose states. In excessive doses, TORECAN may produce extrapyramidal stimulation with the varied symptom complex characteristic of this complication. Ampuls are recommended for **intramuscular injection only.**

References: 1. Codiga, V. A.: A new antiemetic for the treatment of nausea and vomiting associated with roentgen therapy, Int. Rec. Med., 174:375 (June) 1961. 2. Wang, S. C. and Borison, H. L.: The vomiting center: its destruction by radon implantation in dog medulla oblongata, Am. J. Physiol. 166:712 (1951). 3. Wang, S. C. and Borison, H. L.: A new concept of organization of the central emetic mechanism: recent studies on the sites of action of apomorphine, copper sulfate and cardiac glycosides, Gastroenterol. 22:1 (1952). 4. Wang, S. C. and Glaviano, V. V.: Locus of emetic action of morphine and hydergine in dogs, J. Pharmacol. & Exper. Therap. 111:329 (1954). 5. Browne, D. C. and Sparks, R.: Vomiting mechanisms: a clinical study of thiethylperazine, South. M.J., 54:(Sept.) 1961. 6. Browne, D. C. and Sparks, R. D.: Nausea and vomiting, study of thiethylperazine, Scientific Exhibit, American Medical Association Clinical Meeting, Washington, D.C., Nov. 28 (1960). 7. Maritano, M., Guerrieri, S., Menesini, R.: Prophylaxis and therapy of vomiting, Minerva anest. 26:343 (1960). 8. Modell, W.: Drugs of choice 1960-1961. C. V. Mosby Co., St. Louis, 1960, p. 339.

SANDOZ ORIGINAL RESEARCH SERVING THE PHYSICIAN

acts on the True Vomiting Center

TORECAN®

Thiethylperazine Maleate

2-ethyl-mercapto-10-[3'-(1''-methyl-piperazinyl-4'')-propyl-1'] phenothiazine dimaleate

FOR THE HYPERTENSIVE..

HYPERTENSIVE INVALIDISM:

headache
dizziness
palpitations
tachycardia
anginal pain
anxiety
organic changes
edema
restricted salt intake

THE DIFFERENCE

LIFE BECOMES MORE LIVABLE WHEN YOU PRESCRIBE

DIUPRES®

DIURIL® (CHLOROTHIAZIDE) **WITH RESERPINE**

- the first "wide range" antihypertensive
- effective by itself in a majority of patients with mild or moderate hypertension, and even in many with severe hypertension
- should other drugs need to be added, they can be given in much lower than usual dosage

MORE NORMAL LIFE:

hypertensive symptoms are usually relieved

anginal pain may be reduced in incidence and severity

anxiety and tension are usually allayed

organic changes may be arrested or reversed

dietary sodium can usually be liberalized

IS DIUPRES

DIUPRES-250
250 mg. DIURIL chlorothiazide, 0.125 mg. reserpine per tablet. One tablet one to four times a day.*

DIUPRES-500
500 mg. DIURIL chlorothiazide, 0.125 mg. reserpine per tablet. One tablet one to three times a day.*

*It is essential to reduce the dosage of other antihypertensive agents, particularly the ganglion-blockers, by at least 50 per cent immediately upon addition of these agents or of Diupres Tablets to the regimen.

Before prescribing or administering DIUPRES, the physician should consult the detailed information on use accompanying the package or available on request.

MSD **MERCK SHARP & DOHME**
DIVISION OF MERCK & CO., INC., WEST POINT, PA.

DIUPRES AND DIURIL
ARE TRADEMARKS OF MERCK & CO., INC.

NEW

Dimetapp® Extentabs®

let your sinusitis, allergy and U.R.I. patients breathe easier!

DIMETAPP Extentabs contain Dimetane®(parabromdylamine [brompheniramine] maleate) 12 mg., phenylephrine HCl 15 mg., and phenylpropanolamine HCl 15 mg., a proved antihistamine and two outstanding decongestants. The dependable Extentab form provides sustained relief from the stuffiness, drip and congestion of sinusitis, colds and U. R. I. for 10-12 hours with a single dose.

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MAKING TODAY'S MEDICINES WITH INTEGRITY SEEKING TOMORROW'S WITH PERSISTENCE

Schering

First total regimen in athlete's foot

ADVICIN is the first topical preparation to combine the proved *anhidrotic* and *antipruritic* benefits of an anticholinergic with widely accepted *fungicidal* and *keratolytic* agents... ADVICIN reduces local sweating, helps keep feet dry... helps relieve itching promptly... has a pleasant medicinal scent... may shorten the fungous-clearing time required with oral FULVICIN. *Supplied:* ADVICIN Powder—2 ounce can—for daytime use. ADVICIN Cream—50 gram tube—for nighttime use. For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, New Jersey.

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NEW

advicin™

TOPICAL

first topical fungicide with sweat-inhibiting action*

2-way antifungal attack in a moisture-controlled, antifungal environment

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first orally effective antifungal antibiotic for ringworm

*ADVICIN contains diphemanil methylsulfate (PRANTAL®) 2%, undecylenic acid 5%, and salicylic acid 3%.

Now! 2 appetizing foods make serum cholesterol control easier, more effective than ever!

Your Patients Can Enjoy Fine Foods With Minimum Diet Changes!

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Leading authorities agree that where reduction of serum cholesterol levels is indicated, fat intake should not exceed ⅓ of total calories and of this, at least ⅓ should be polyunsaturated fats.

Polyunsaturated fats, such as those found in corn oil, are rich in the linoleates which are important in reducing serum cholesterol levels. This has been proven time and again in nutritional studies of hypercholesterolemia. Mazola Margarine and Mazola Corn Oil have outstanding P/S (polyunsaturate to saturate) ratios. Thus the hypercholesterolemic patient can usually enjoy the same appetizing foods as the rest of the family.

Mazola Corn Oil is unexcelled in polyunsaturates and lowest in saturates of all leading brands of vegetable oils. Mazola's P/S ratio is far higher than that of any other leading food oil. Your patient will find Mazola Corn Oil ideally suited for salad dressings and frying; also for baking wherever *liquid* shortenings are called for in the recipe.

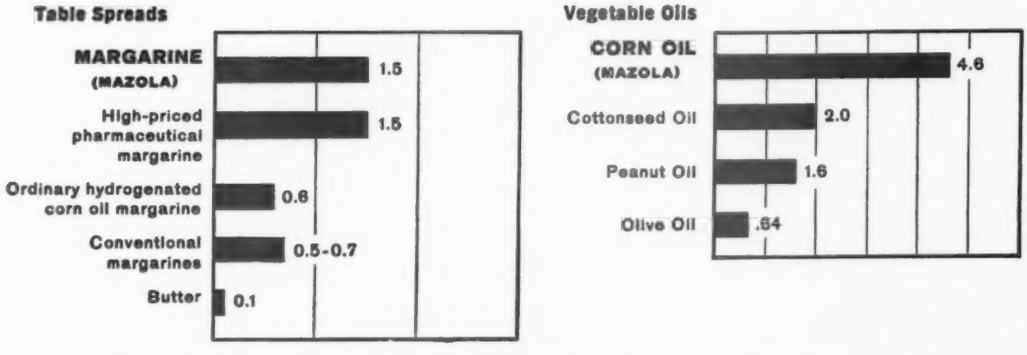
Mazola Margarine contains *liquid* Mazola Corn Oil as a major ingredient. This corn oil is not hydrogenated, thereby preserving its rich content of linoleates. Mazola Margarine contains 2 to 3 times as much natural linoleates as any other margarine readily available in grocery stores from coast to coast. Its taste, color and handling characteristics are unexcelled.

AVERAGE COMPOSITIONS OF MAZOLA® MARGARINE AND MAZOLA® CORN OIL
(All figures are in grams.)

	MAZOLA MARGARINE		MAZOLA CORN OIL	
	100 grams	2 oz. (4 tbsp.)	100 grams	1 fl. oz. (2 tbsp.)
Fatty Acids				
Polyunsaturated	21	12	51	14
Monounsaturated	40	23	32	9
Saturated	14	8	11	3
Natural Sitosterols	0.5	0.3	1	0.3
Natural Tocopherols	0.08	0.045	0.08	0.020
Cholesterol	none	none	none	none
Sodium	0.9	0.5	none	none

MAZOLA MARGARINE—410 Calories/2 oz.; Iodine Value—96
MAZOLA CORN OIL—250 Calories/fl. oz.; Iodine Value—124

RATIO OF POLYUNSATURATES/SATURATES
(Average values.)



Write *for a copy of* A MEAL PATTERN FOR THE HYPERCHOLESTEROLEMIC PATIENT. *Contains 25 individual instruction sheets for your patients.*

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'ACTIFED'®

Decongestant / Antihistamine

THE POTENTIATED DECONGESTANT

provides symptomatic relief of nasal congestion and rhinorrhea of allergic or infectious origin Many patients whose symptoms are inadequately controlled by decongestants or antihistamines alone respond promptly and favorably to 'ACTIFED'.

'ACTIFED' contains:	in each Tablet	in each tsp. Syrup
'Actidil'® brand Triprolidine Hydrochloride	2.5 mg.	1.25 mg.
'Sudafed'® brand Pseudoephedrine Hydrochloride	60 mg.	30 mg.

safe and effective for patients of all ages suffering from upper respiratory tract congestion

DOSAGE

	TABLETS	SYRUP (5 cc. tsp.)	
Adults and older children	1	2	three times daily
Children 4 months to 6 years of age	½	1	
Infants through 3 months	–	½	

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

They Bounce Back Fast with TYLENOL®

acetaminophen

antipyretic / analgesic

He's the same young patient who was feverish and listless yesterday—Tylenol quickly brings fever and discomfort under control.

Tylenol is safe, exceptionally free from side effects[1,2]...well tolerated by children.[1]

AFTER T & A, the gentle antifebrile-analgesic action of Tylenol reduces restlessness, aids recuperation.

TYLENOL ELIXIR—120 mg. (2 gr.) per 5 cc.; 4 and 12 fl. oz. bottles

TYLENOL DROPS—60 mg. (1 gr.) per 0.6 cc.; 15 cc. bottles with calibrated droppers

Also available for adults and older children:

Tablets TYLENOL—5 gr. (300 mg.)

1. Cornely, D. A., and Ritter, J. A.: N-acetyl-p-aminophenol (Tylenol Elixir) as a Pediatric Antipyretic-Analgesic, J.A.M.A. *160*:1219-1221 (April 7) 1956.
2. Mintz, A. A.: Management of the Febrile Child, J. Ky. Acad. Gen. Pract. *5*:26-31 (January) 1959.

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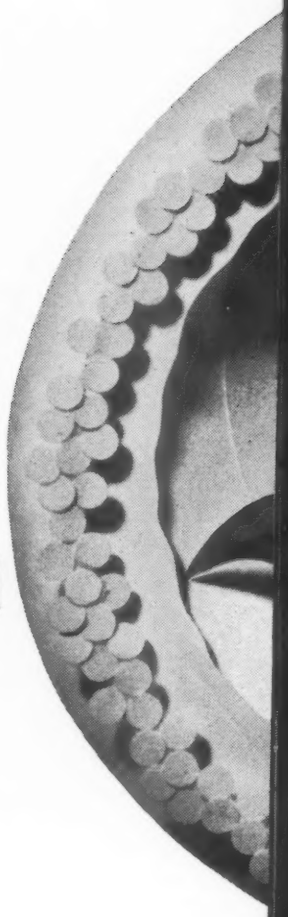

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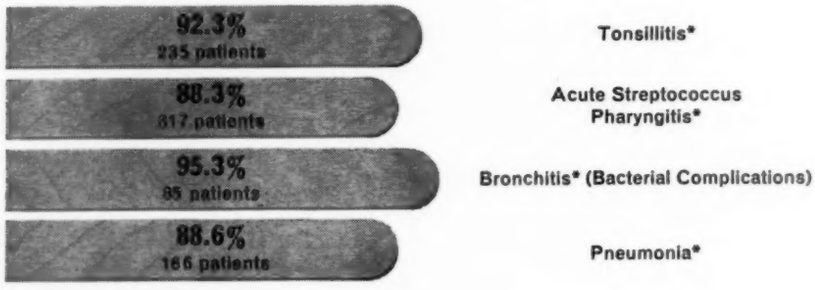

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The American Journal of Medicine

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Editorial

The Variability of Blood Viscosity*

WITHIN the different parts of the human vascular system the viscosity of blood has many different values. Studies of the flow properties of freshly drawn whole blood have shown that its viscosity is dependent upon the flow velocity and the dimensions of the conducting vessel. That science which concerns itself primarily with the study of these properties of fluid flow is known as rheology. Rheology specifically is defined as the study of the deformation and flow of matter. Although a perusal of the world's literature concerning rheologic investigations would clearly demonstrate a preponderant contribution by chemical and civil engineers, it was the French physician, J. L. M. Poiseuille, who in 1840 first defined the basic law of flow of liquids through capillary tubes. His earliest reports concerned direct observations of blood flow through the mesenteric vessels of small animals. During his later experiments with glass capillary tubes, from which his law is derived, he resorted to water as his experimental fluid. Sixty-six years passed before the next rheologic study of blood appeared. In 1906 Denning and Watson [*1*] reported that the apparent viscosity of blood was dependent upon the diameter of the tube in which it flowed, while a year later Hess [*2*] stated that blood viscosity was dependent upon the velocity of flow within the tube. Hess also noted that viscosity values changed greatly when velocity was altered over a range of low flow rates, and that changes in velocity at high rates of flow resulted in comparatively small changes in viscosity. In terms of fluid mechanics, these observations were very early descriptions of the flow-dependent characteristics of blood viscosity. Subsequent to these early studies a number of workers pointed out that the viscosity of blood is anomalous, i.e., its viscosity does not vary proportionately with equal increments of change in the driving pressure. The Law of Poiseuille† refers only to fluids the viscosity of which is constant at different rates of (laminar) flow and therefore this law is inapplicable for the deterrmination of viscosity of fluids such as blood. Fåhraeus and Lindquist [*3*] studied the "anomaly of blood viscosity" by use of a series of capillary tubes of which the ratio of length to radius was kept constant. They stated that in the smaller tubes (0.3 mm. diameter and less) the decrease in viscosity was due to an increased concentration of red cells in the central axial stream. The number of studies which appear to support an axial streaming phenomenon have led to the eponym of the "Fåhraeus-Lindquist effect." Bayliss [*4*], whose work and publications upon blood viscosity are the most comprehensive and critical of the many we have reviewed, has discussed the validity of the observations of the axial streaming of red cells. He agrees that the reduced concentration of cells at the wall of a vessel (because

† $Q = \dfrac{(P_1 - P_2)\pi r^4}{8\,L\eta}$

P = pressure (dynes/cm.²)
Q = flow (ml./sec.)
η = viscosity (dyne sec./cm.²) (poise)
r = radius (cm.)
L = tube length (cm.)

* Manuscript received June 27, 1961.

they cannot enter the wall) justifies the conclusion that there is an exclusion effect at the wall. Earlier, the validity of such a consideration was derived for rigid spheres in suspension by Vand [5] and is known as the "Vand wall effect." Bayliss points out, however, that the presence of an extensive plasma layer at the vessel wall does not appear to be proved for whole blood with red cell concentrations above 40 per cent.

Although rheologists and physiologists have been aware that the variability of blood viscosity is due to quantifiable physical factors, it would appear that many workers in the field of cardiovascular research remain unaware of certain basic principles of flow mechanics as they apply to blood. The misinterpretation of one of these principles involves the derivation of the Poiseuille formula. Implicit in the first step of this derivation is the assumption that the fluid viscosity is identical at every place in the tube, independent of the local flow stresses. Rheologists quantitate fluid flow properties in terms of shearing stresses and rates of shear. Considering the increasing attention being devoted to the biologic applications of rheology, it is apparent that the terms "shear stress" and "shear rate" will be referred to in the medical literature with increasing frequency. Briefly, the definition of these terms is as follows: Shear stress is that tangential force per unit area applied to a fluid plane to cause it to slide or skid over a neighboring plane, thereby producing fluid flow. It is measured in units of dynes/square centimeter. It relates to the frictional forces within a fluid during flow and is determined in magnitude by the viscous characteristics of the fluid. The other essential parameter in any quantitation of rheologic behavior is the rate at which the shear stress occurs or is applied. Shear rate is an expression of the gradient of velocity between the adjacent planes of layers of fluid during flow, i.e., how fast one plane moves with respect to its neighbor. Specifically, shear rate is defined in increments of velocity of one plane moving over another per unit distance between them at 90 degrees to the plane of flow. Velocity in centimeters/second divided by distance in centimeters results in reciprocal or inverse seconds ($sec.^{-1}$). Shear rate is always expressed in these units and is often referred to as its equivalent, the velocity gradient. By knowing the ratio of shear stress to shear rate the flow properties of any fluid can be quantified. This expression of the ratio of these forces was precisely the way viscosity was first defined by Isaac Newton 300 years ago. All fluids are characterized rheologically by the manner in which this ratio changes with changing rates of shear. Knowing shear stress-shear rate values not only permits quantitation of the general term "anomalous viscosity," but also allows comparison of data between different studies of hemodynamics. A broader discussion of the practical limitations of capillary tube viscometers for the analysis of fluids with a shear stress-shear rate relationship which is not fixed has been presented elsewhere [6]. A major factor influencing the degree of variability of this ratio is the physical characteristics and interrelationships of the elements that make up the fluid. If all the elements are small, equal in size, and the fluid homogeneous, the ratio of shear stress to shear rate will usually be constant. Such simple fluids are known rheologically as Newtonian fluids. Those with large-sized molecular constituents or high concentrations of suspended matter will generally have a varying ratio of these values of shear and are known generally as non-Newtonian fluids. The complexity of a fluid with a 40 per cent suspension of (red) cells and a 7 per cent concentration of macromolecular substances (protein) precludes, for practical purposes, the quantitation of shear stress to shear rate in a capillary tube. Viscometers in which shear stress and shear rate can be measured or derived in absolute terms over a broad range of values have long been available, although their use by physiologists has been quite limited. As noted, Poiseuille in his capillary studies used water as his test fluid; one in which shear stress-shear rate relationships are constant and can be analyzed by means of a capillary tube viscometer. Fluids such as blood, and many industrially important fluids, such as paint, ink, clay suspensions and soaps, do not bear a constant proportionality between shear stress and shear rate; therefore, shear stress must be measured at specified rates of shear.

Perhaps in the desire to approximate the geometry of the vascular system, cardiologists have been reluctant to give up a model so closely resembling the living system. Many who have realized the rheologic limitations of such a system have continued to justify capillary viscometric technics on the basis that the plasma is the rheologically important fluid since it flows as a slippage layer at the vessel wall and that it is a

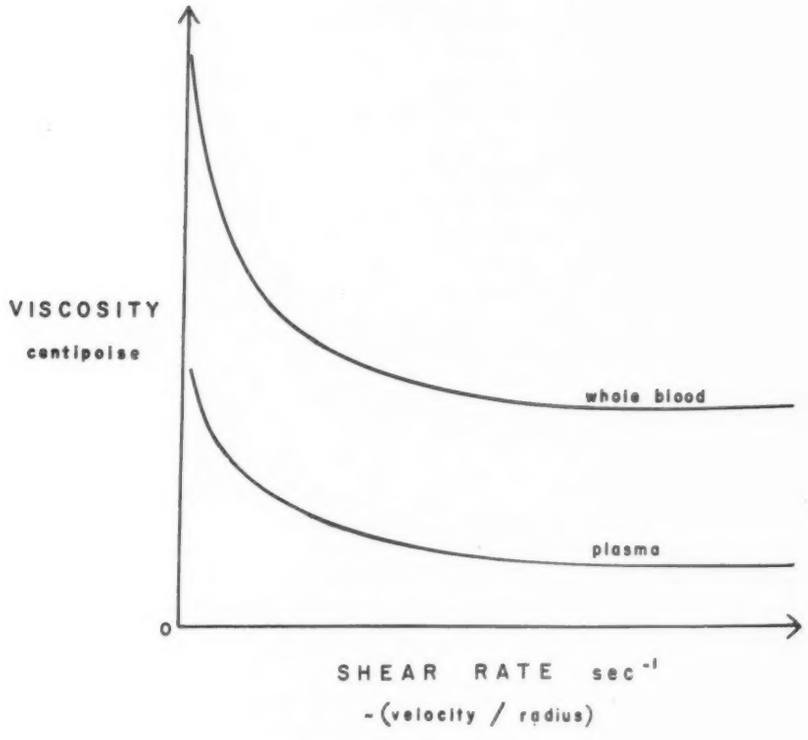

FIG. 1

Newtonian fluid. There are two misconceptions in such a rationalization: (1) The shear stress-shear rate relationships exist between all layers of fluid and not just between the fluid and the wall; (2) the monomolecular layer at the wall theoretically is not in motion; each adjacent layer, as the central axis is approached, is moving a bit faster than its more peripheral neighbor.

The use of *in vitro* anticoagulants profoundly decreases the non-Newtonian flow properties of blood and plasma. The large number of studies on blood and plasma viscosity have not taken this anticoagulant effect into consideration. Considering the extent to which (*in vivo*) anticoagulant therapy is employed, it is apparent that studies of the *in vivo* effects of anticoagulants upon the entire viscosity shear rate relationships would be of clinical significance. It has been our impression, from studies using intravenous heparin, that this agent has significant effects upon the viscous properties of blood *in vivo*, although in normal subjects the degree of change is not uniform. There are, to be sure, many reports of the effects of anticoagulant agents upon blood viscosity analyzed by means of capillary tube systems.

For practical purposes shear rate may be approximated for any part of the vascular system by relating the mean flow velocity to the radius of the vessel. Shear rate values can be estimated for a given vessel by use of the formula $4\ \bar{V}/r$ where $\bar{V}$ equals mean velocity in centimeters/second and r the radius in centimeters. The major limitation of this formula is that it applies only for Newtonian fluids. Also the radii of smaller vessels are known only in approximate values. If these limitations are accepted, not to mention those of the living state of non-parallel walls, pulsatile flow, and moment to moment variations in vasomotor tone, then the shear rate in the ascending aorta in normal man at rest can be shown to be between 100 and 300 inverse seconds. Less reliable is the calculation of shear rate in the medium-sized arterioles, which can be estimated to be from five to twenty-five inverse seconds. From these conjectural ranges of values of shear rate in the normal subject, it can be shown that, with the knowledge of the viscosity-shear rate relationships of whole blood (Fig. 1), blood viscosity in the aorta will be the lowest of any part of the vascular system, approaching a maximum as the arteriole is approached. The arteriole is held as the upper limit in this progression to higher viscosity as the

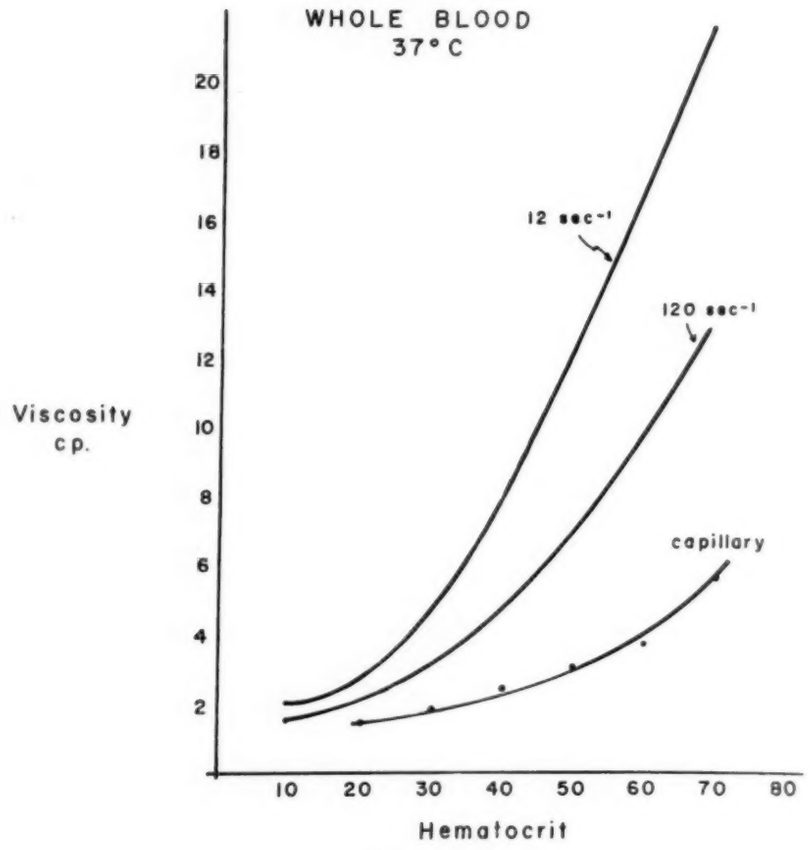

FIG. 2

peripheral vessels are approached. The reason for not extrapolating values for the capillaries is as follows. As blood flows through a vessel whose diameter is but four to five times that of the diameter of the red cell, no longer will the rheologic characteristics depend upon the whole mixture, rather the flow dominating component becomes the plasma itself. This is vividly emphasized in the capillary where "plug flow" appears to exist, in that the red cell moves through a tube barely larger than the cell itself [7]. The effects of a shear rate-dependent fluid upon the character of the red cell motion through a capillary has been discussed elsewhere [8]. The influence of surface tension effects upon the viscosity-shear rate relationships of blood or plasma must be considered when rheological studies are conducted by means of container type viscometers. Suspensions of red cells in normal saline solution at hematocrit values of 30 per cent and higher also demonstrate non-Newtonian properties although somewhat less than that of whole blood of equivalent cellular concentrations.

The principal frame of reference the physician has with respect to blood viscosity is its relationship or dependency upon the hematocrit or red cell concentration. The classic curve depicted by most texts of physiology show a plot of values in which a curvilinear function demonstrates a rapidly rising viscosity value as hematocrit levels exceed 55 volumes per cent. This arbitrary point in the curve is often justification for therapeutic phlebotomy on hydrodynamic principles when a hematocrit value of 55 is exceeded. Studies of viscosity-hematocrit relationships at high and low rates of shear reveal significantly different curves [9]. At low rates of shear, there is a relatively higher viscosity value for a given hematocrit and the curve approximates a linear function. At high shear rates, the curve moves down and to the right with lower values for viscosity at hematocrit levels comparable to those plotted at low rates of shear. (Fig. 2.) Estimating the shear rates from the data presented in the various reports in which capillary tube systems were employed, it can be shown that, generally, these systems operate at very high ranges of shear rate (velocity being

very high in relation to tube radius). A representative capillary tube system with a diameter of 0.8 mm. and a length of 80 to 100 mm. will, with a flow rate of 0.1 cm.^{3}/second approximate a shear rate in the neighborhood of 2,000 inverse seconds. The standard textbook illustration of viscosity-hematocrit relationships is derived from these capillary studies. Comparison of these curves with those of lower shear rate curves reveals that viscosity values for a given hematocrit are considerably less at high rates of shear. The point to be made is that deriving viscosity values from standard reference curves may be meaningless if shear rate values are not noted. Data from capillary tube viscometry probably produce shear rate values in excess of those that are physiologically significant.

The increasing attention being paid to these rheologic matters in the medical arena confirms the prediction of Dr. Scott Blair who stated that there is "no field in which in the near future rheology is more likely to make useful advances than in that concerned with medical problems . . . " As a result particularly of International Conferences and Colloquia on the rheology of blood and other biologic systems, there are now available in recent texts rather comprehensive and lucid discussions of these matters, including the related principles of fluid mechanics. (See, for example, "Flow Properties of Blood," by Copley and Stainsby [*10*] and the chapter by Burton in a recent edition of a textbook of physiology [*11*].) At the Annual Meeting of the Society of Rheology, American Institute of Physics, in Madison, Wisconsin (October 1961) an entire section will be devoted to studies on the rheology of blood. The plan for this meeting confirms our experience that engineers of all types appear to be deeply interested in the application of engineering principles to biology whenever the method or reason for application is presented to them.

Although this discussion has alluded to the effect therapeutic anticoagulant agents (*in vivo*) may have upon the rheologic properties of blood, the discussion has not considered the effects abnormal plasma factors or abnormal concentrations of normal factors, or abnormal red cell configurations might have upon blood flow properties. The main purpose of this brief discussion is to emphasize the need to consider well established physical principles of fluid flow that pertain to complex fluids such as blood and, in particular, to direct attention to the misleading interpretations that can arise when whole blood is considered to be a homogeneous fluid obeying the Poiseuille Law. Clarifying the concept that blood viscosity is flow-dependent in all cases, and that plasma viscosity is the rheologically critical fluid in the microcirculation, provides a stimulus for the reconsideration of many important circulatory and hemodynamic phenomena.

ROE E. WELLS, JR., M.D.
Departments of Medicine
Peter Bent Brigham Hospital
and Harvard Medical School
and the Howard Hughes Medical Institute,
Boston, Massachusetts
and EDWARD W. MERRILL, D.SC.
Department of Chemical Engineering
Massachusetts Institute of Technology
Cambridge, Massachusetts

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Clinical Studies

Studies of Chronic Familial Non-Hemolytic Jaundice with Conjugated Bilirubin in the Serum with and without an Unidentified Pigment in the Liver Cells*

I. M. Arias, M.D.
New York, New York

Chronic familial non-hemolytic jaundice with conjugated bilirubin as well as free bilirubin in the plasma has been described in association with an unidentified pigment in the liver cells by Dubin and Johnson [1] and Sprinz and Nelson [2]. Rotor et al. [3], Stransky [4], Schiff et al. [5], Haverback and Wirtschafter [6] and Peck et al. [7] have reported cases of chronic familial non-hemolytic jaundice in which serum gives a direct van den Bergh reaction but in which the liver cells are free of abnormal pigment. The interrelationship, if any, between cases of familial jaundice of this type with hepatic pigmentation (i.e., the Dubin-Johnson syndrome) and those without pigmentation (i.e., the Rotor syndrome) is unknown. The observation that the amount of intrahepatic pigmentation in cases of the Dubin-Johnson syndrome varies considerably [8] suggests that these two syndromes may represent varied manifestations of a common functional defect.

This study concerns three related patients with chronic idiopathic jaundice associated with conjugated bilirubin in the serum. Two patients had abnormal hepatic pigmentation, and a diagnosis of chronic idiopathic jaundice of the Dubin-Johnson type was made. A specimen of the liver was obtained from the third patient on four separate occasions and detailed histologic examination failed to reveal the presence of any abnormal intrahepatic pigment. Further studies were performed in an attempt to learn more from this occurrence.

CASE REPORTS

Case 1. A Puerto Rican housepainter (D. A.), was well until the age of twenty-seven when in November 1957 he was admitted to the Bronx Veterans Administration Hospital because of fever, chills, lumbar backache, non-productive cough, diaphoresis and scleral icterus. The acute symptomatology disappeared within forty-eight hours and was attributed to a viral infection of the respiratory tract. Scleral icterus persisted. The patient stated that his eyes had been yellow for as long as he could remember; this observation was confirmed on subsequent interview with several of his friends and relatives. There was no previous history of abdominal pain, pruritus, dark urine or lightly colored stools. The patient had not experienced any illness which required bed rest or any temporary cessation of work.

Physical examination showed a well nourished, well developed Puerto Rican man with slightly icteric skin, mucous membranes and sclerae. A smooth non-tender liver edge was palpable 2 fingerbreadths below the right costal margin on deep inspiration. Following subsidence of the acute infection of the respiratory tract the following examinations were performed, with normal results: urinalysis, complete blood count, erythrocyte sedimentation rate, reticulocyte count, blood urea nitrogen, fasting blood sugar, concentration and electrophoresis of serum proteins, bleeding time, clotting time, clot retraction, platelet count,

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prothrombin time, serum alkaline phosphatase, cholesterol and cholesterol esters, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, thymol turbidity, cephalin cholesterol flocculation and urine urobilinogen. A roentgenogram of the chest and barium examination of the upper and lower gastrointestinal tract were within normal limits. Bilirubin was intermittently present in the urine. The serum bilirubin concentration was 3.1 mg. per cent, of which 1.5 mg. per cent gave the direct van den Bergh reaction. Results of a blood Wassermann test and a rectal biopsy for schistosomiasis were negative. Forty-five minutes following the intravenous injection of 5 mg. of bromsulphalein per kg. of body weight, there was 5 per cent bromsulphalein retention. Oral cholecystography did not reveal contrast medium in the gallbladder on two occasions following a single dose of contrast medium. Following ingestion of a double dose of the contrast medium, a faintly opacified gallbladder was visualized. Aspiration liver biopsy was performed and an abundant amount of an intracellular pigment of the Dubin-Johnson type was observed. A second liver biopsy was performed two years later.

CASE II. A forty-two year old Puerto Rican housewife (M. R.) the paternal aunt of patient D. A. (Case I), had been in good health until March 1945. At that time she entered Bellevue Hospital for investigation of postprandial epigastric distress and mild chronic icterus of approximately one to two years' duration.

On physical examination she was a thin, well nourished Puerto Rican woman in no acute distress. Scleral icterus and moderate tenderness of the upper right quadrant of the abdomen were observed. Complete blood count, urinalysis, erythrocyte sedimentation rate, fasting blood sugar, prothrombin time, concentration of serum proteins, cholesterol, thymol turbidity, cephalin cholesterol flocculation, alkaline phosphatase, qualitative urine urobilinogen excretion, roentgenogram of the chest and barium examination of the upper gastrointestinal tract were within normal limits. Stool examination for ova and parasites was negative. There was no bilirubinuria. The gallbladder visualized faintly on oral cholecystography and several small radiopaque gallstones were noted as a result of which cholecystectomy was subsequently performed. At laparotomy the liver was described as "unusually black, smooth and not cirrhotic." A biopsy specimen revealed intracellular pigment of the Dubin-Johnson type. Six weeks later the serum bilirubin concentration was 3.4 mg. per cent of which 1.6 mg. per cent reacted directly with diazotized sulfanilic acid. Two years later bromsulphalein retention forty-five minutes after the intravenous administration of 5 mg. bromsulphalein per kg. body weight was 11 per cent. A second liver biopsy was performed. Similar histologic findings were observed.

CASE III. A thirty-five year old Puerto Rican housepainter (D. R. A.), the brother of patient D. A. (Case I), was studied at the Bronx Municipal Hospital Center in May 1959. Jaundice was first noted by a physician in Puerto Rico eleven years previously. His general health was normal except for two episodes of viral pneumonia when the patient was twenty-eight and thirty-two years old. As a child he was treated for intestinal worms with apparent success.

Physical examination revealed a well developed, muscular Puerto Rican man with icterus of the mucous membranes and sclerae. A smooth, non-tender liver edge was palpable at the right costal margin on deep inspiration. The following examinations were performed, with normal results: urinalysis, complete blood count, erythrocyte sedimentation rate, serologic test for syphilis, stool guaiac test and examination for ova and parasites, blood urea nitrogen, fasting blood sugar, thymol turbidity test, concentration of serum proteins, electrophoresis of serum proteins, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, cholesterol and cholesterol esters, prothrombin time, and leucine amino peptidase. Roentgenographic studies of the upper and lower gastrointestinal tract were within normal limits. There was visualization of the gallbladder and slight visualization of the common bile duct following ingestion of a double dose of Telepaque.® The result of the cephalin cholesterol flocculation test fluctuated from 1 to 3 plus. Serum alkaline phosphatase activity ranged from 3.4 to 6.7 Bodansky units. The urine intermittently contained bilirubin. Semi-quantitative urine urobilinogen excretion was normal. Bromsulphalein retention forty-five minutes after the intravenous injection of 5 mg. of bromsulphalein per kg. of body weight ranged from 23 to 29 per cent on three occasions. The serum total bilirubin concentration was 5.3 mg. per cent, of which 2.4 mg. per cent gave the direct van den Bergh reaction. Aspiration liver biopsy was performed on this and three subsequent occasions. Detailed study failed to reveal the presence of any abnormal intracellular pigmentation.

Hereditary Characteristics. The hereditary characteristics of this family with non-hemolytic jaundice are presented in Figure 1. The father of patients D. A. (Case I) and D. R. A. (Case II), is said to have had intermittent jaundice for many years but was unavailable for study. Five anicteric siblings were also not available for study. The two children of patient D. A. (Case I) and the two children of patient M. R. (Case II) had normal serum bilirubin concentrations and normal bromsulphalein retention forty-five minutes following the intravenous injection of 5 mg. of bromsulphalein per kg. of body weight.

Experimental Procedure. The following were estimated: (1) erythrocyte survival, using the

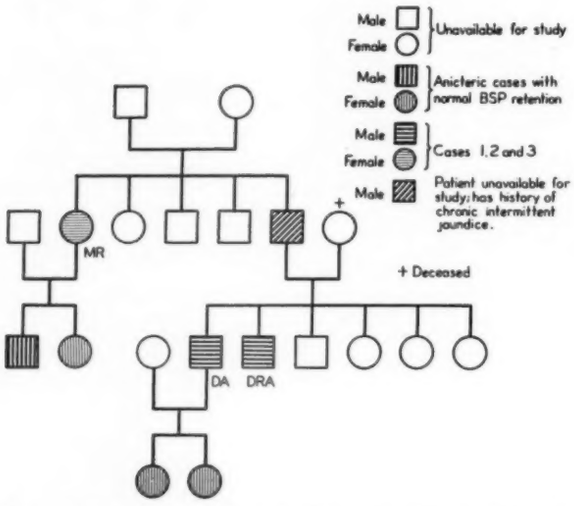

FIG. 1. Hereditary characteristics of chronic familial jaundice.

Cr^{51} labeling technic of Mollison and Veall [*9*]; (2) quantitative urine and fecal urobilinogen excretion by the method of Watson et al. [*10*]; (3) distribution of plasma bile pigments using the method of Billing [*11*]; (4) concentration of dipyrrol azo pigments A and B following the coupling of bilirubin in the serum with diazotized sulfanilic acid, using the chromatographic method described by Schmid [*12*]; (5) the percentage of a 1 gm. oral dose of menthol which was excreted in the urine as menthol glucuronide in the subsequent four hours, using the method of Williams [*13*]; (6) hepatic glucuronyl transferase activity, using 4 methyl umbelliferone as a glucuronide receptor according to the method described by Arias [*14*]; (7) the hepatic relative storage capacity and Tm for bromsulphalein, using the method of Wheeler et al. [*15*]; and (8) the concentration of free and conjugated bromsulphalein in the plasma following the intravenous injection of 5 mg. of bromsulphalein per kg. of body weight, using the method of Grodsky [*16*]. Histochemical* and electron micrographic studies of liver biopsy specimens obtained in Cases I and III were performed by Drs. Alex Novikoff and Edward Essner and Mr. Sidney Goldfisher.

* Specimens of liver were obtained by aspiration biopsy and subjected to the following staining reactions [*32*]: hematoxylin and eosin, oil red orange, ATPase, acid phosphatase, alkaline phosphatase, lactic dehydrogenase, DPNH cytochrome C reductase and 5-nucleotidase.

EXPERIMENTAL RESULTS

The results are presented in Table I. The half-time for survival of Cr^{51}-labelled erythrocytes was normal in the two patients (Cases I and II) in whom this was estimated. Estimations of fecal and urinary urobilinogen excretion were within normal limits. The plasma bile pigments were distributed as bilirubin 38 to 50 per cent, pigment I 28 to 42 per cent and pigment II 20 to 24 per cent. Forty-five to 55 per cent of the total dipyrrol azo pigments was present as azo pigment A and 45 to 55 per cent as azo pigment B. In each case chromatography of azo pigment B after alkaline hydrolysis revealed from 31 to 41 per cent to be alkali-stable. From 38 to 48 per cent of azo pigment B remained after enzymatic hydrolysis by beta-glucuronidase. The three patients (Cases I, II and III) excreted 28, 38 and 46 per cent, respectively, of an ingested 1 gm. dose of menthol in the urine, as menthol glucuronide, in the subsequent four hours. These results are within 2 standard deviations of the mean for normal persons of approximately the same age and sex. Assays of hepatic glucuronyl transferase activity, performed in duplicate were within normal limits. The relative hepatic storage of bromsulphalein (expressed as milligrams of bromsulphalein stored per milligrams per cent bromsulphalein in plasma) was within normal limits in each patient. The hepatic Tm for bromsulphalein was markedly reduced in each of the three subjects. The measurements of hepatic Tm for bromsulphalein were minus 0.9, plus 0.3 and plus 0.3 mg. per minute, respectively, for each of the three patients as compared with 9.5 plus or minus 1.9 mg. per minute in normal subjects [*15*]. Serum samples were obtained forty-five and 100 minutes after the intravenous injection of 5 mg. of bromsulphalein per kg. of body weight. At forty-five minutes from 10 to 20 per cent of the bromsulphalein in the serum was present as conjugated bromsulphalein and from 80 to 90 per cent as free bromsulphalein. At 100 minutes, from 50 to 78 per cent of the bromsulphalein in the serum was present as conjugated bromsulphalein and from 22 to 50 per cent was free bromsulphalein.

Histologic studies in Cases I and II revealed abundant amounts of a coarse yellow-brown pigment in the liver cells. The pigment gave a histochemical staining reaction for acid phosphatase activity. Other histochemical staining reactions

TABLE I

EXPERIMENTAL RESULTS

Case No.	Erythrocyte Survival T/2 Cr^{51} (days)	Urobilinogen Excretion (mg./24 hr.)		Serum Bilirubin Concentration (mg. %)		Plasma Bile Pigments (%)			Dipyrrol Azo Pigment		Azo B Remaining after Hydrolysis %		Menthol Tolerance Test (%)	Hepatic Glucuronyl Transferase (units)	Hepatic Tm for Bromsulphalein (mg./min.)	Hepatic Storage for Bromsulphalein (mg./mg. %)	Light Microscopy	Electron Microscopy
		Urinary	Fecal	Direct-reacting	Total	Bilirubin	Pigment I	Pigment II	Azo A	Azo B	Alkaline	Beta-glucuronidase						
I	28	1.6	126	1.5	3.1	38	42	20	50	50	31	38	28	197	−0.9*	56*	Abundant acid phosphatase positive coarse pigment in liver cells	Intercellular pigment in lysomes
II	30	1.0	190	2.3	4.4	50	28	22	55	45	41	48	38	206	+0.3*	47*	Abundant coarse pigment in liver cells	...
III	...	2.4	147	2.4	5.3	45	31	24	45	55	35	40	46	180	+0.3	68	No abnormal hepatic pigmentation; increased pericanalicular acid phosphatase activity; no staining reaction for alkaline phosphatase activity	No pigment within liver cells Increased pericanalicular lysosomes
Normal	27–30	0.2–3.0	80–300	...	...	...	...	...	...	...	...	...	39.0 + 7.2 of ingested 1 gm. dose of menthol excreted as menthol glucuronide in the urine in subsequent four hours	176–250 (1 unit equals 1 mμ M 4 methyl umbelliferone glucuronide formed/mg. of liver nitrogen/hour)	9.5 + 1.9 min [15]	63 + 25 [15]	...	...

* Performed by H. O. Wheeler and associates and previously reported [5].

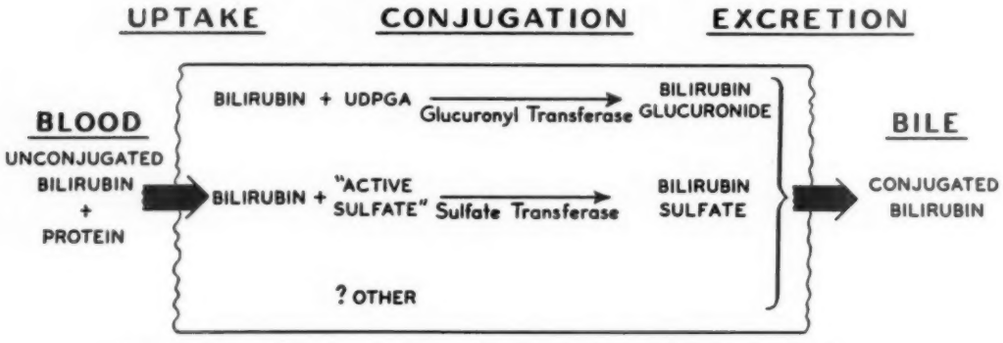

FIG. 2. Schematic representation of the metabolism of bilirubin in the liver.

were within normal limits.* In Case III no abnormal hepatic pigmentation was observed in four liver biopsy specimens. Acid phosphatase staining reaction was abundant in close proximity to the bile canaliculi, particularly in the periportal areas of the liver. No staining reaction for alkaline phosphatase activity was demonstrable. Other histochemical staining reactions were within normal limits.*

Electron microscopy of a liver biopsy specimen in Case I revealed numerous coarse pericanalicular bodies (lysosomes) which contained the electron-dense abnormal pigment. The remaining intracellular components of the liver cells appeared to be normal. In Case III electron microscopic examination failed to reveal any pigmentation. The pericanalicular lysosmes appeared increased in numbers and in dispersion throughout the cell.

COMMENTS

It has been postulated that jaundice in the Dubin-Johnson and Rotor syndromes results from an impairment of hepatic excretory function [*1,5,6*]. The general mechanism by which bilirubin is metabolized by the liver is illustrated in Figure 2 and has recently been reviewed [*17*]. Conjugation of bilirubin, primarily with glucuronic acid, is required for the excretion of bilirubin in the bile [*18*]. The mechanisms which control the excretion of bilirubin conjugates into the bile are poorly understood. In normal rats the capacity to excrete conjugated bilirubin appears to be the limiting factor in the over-all metabolism of bilirubin by rat liver [*19*]. The administration of norethandrolone (Nilevar®) to rats [*20*] and the administration of Icterogenin, an alkaloid obtained from Lippia rehmanni, to rats [*22*] and rabbits [*21*] results in a reduced capacity of the liver to excrete conjugated bilirubin, unassociated with reduction in hepatic UDPG* dehydrogenase or glucuronyl transferase activities. These observations suggest that norethandrolone and Icterogenin may interfere with the process by which conjugated bilirubin is transported from the liver cell into the bile. Characterization of the proposed defect in hepatic excretory function in the Dubin-Johnson and Rotor syndromes could result in better understanding of normal hepatic excretory function. In this connection it is important to establish whether the Dubin-Johnson and the Rotor syndromes represent different disease entities or varied expressivity of a common functional defect.

Only five reports of chronic idiopathic jaundice with conjugated bilirubin in the serum and normal liver histology have been published [*3–7*]. Nevertheless, it appears useful to compare the observed clinical, laboratory and pathologic features with those reported by Dubin [*23*], in a review of fifty cases of chronic idiopathic jaundice with unidentified pigment in the liver cells.

The Dubin-Johnson syndrome has been found in both sexes in a widespread ethnic and geographic distribution. Approximately one-third of the patients have a familial history of jaundice of a similar type. The age of onset of jaundice varies from birth to forty years but the greatest incidence is in the second and third decades of life. Approximately 80 per cent of the patients complain of vague abdominal pain, weakness, nausea, anorexia or diarrhea. The remainder are asymptomatic. Fluctuating jaundice occurs in all patients and less than half are found to have a large liver, dark urine or pale stools. Laboratory study has revealed normal hematologic findings including erythrocyte survival and fecal urobilinogen excretion; fluctuating and inter-

* See footnote on p. 512.

* Uridine diphosphate glucose.

mittently increased urinary urobilinogen excretion and serum bilirubin concentrations ranging from 2.4 to 19 mg. per cent of which 26 to 86 per cent reacts directly with diazotized sulfanilic acid. Intermittently positive reaction to the cephalin cholesterol flocculation and thymol turbidity tests and increased alkaline phosphatase activity have been observed. Oral cholecystography reveals either non-visualization or faint visualization of the gallbladder. The biliary excretion of conjugated bromsulphalein is impaired and results in re-entry of some of the conjugated bromsulphalein from the liver into the blood and excretion of an excess of conjugated bromsulphalein by the kidney [*24*]. The uptake of bromsulphalein by the liver during the initial thirty-minute period after the injection appears to be normal [*24*]. Menthol tolerance tests of glucuronide conjugation and *in vitro* assay of hepatic glucuronyl transferase activity are within normal limits. Bromsulphalein retention following the intravenous injection of 5 mg. of bromsulphalein per kg. of body weight is occasionally normal; however, usually the retention is between 10 and 20 per cent. Mandema et al. [*24*] observed a subsequent rise in bromsulphalein concentration in the plasma following the initial disappearance. Wegmann et al. [*25*] found that the secondary rise is due primarily to the presence of bromsulphalein conjugates. Liver histologic examination reveals varied amounts of a coarsely granular brown pigment in the parenchymal cells in a central lobular distribution [*1,2*]. Dubin has stated that "the amount of pigment in the liver does not fluctuate in any given case. Apparently the liver becomes saturated with the pigment which it cannot excrete and retains it even during remissions when jaundice disappears" [*23*]. Wolf et al. [*8*] studied eight members of two Puerto Rican families who had chronic idiopathic jaundice of the Dubin-Johnson type. The amount and distribution of the abnormal pigment varied considerably in the eight cases. In some, only a very small amount of hepatic pigment was observed. This observation suggests that the hepatic pigment *per se* does not produce chronic idiopathic jaundice and confirms previous observations that the amount of pigment present varies considerably in different cases [*23*].

The clinical manifestations in the reported cases of chronic idiopathic jaundice with conjugated bilirubin in the serum and no abnormal hepatic pigmentation may be summarized as follows: Both sexes are represented. Jaundice occurred first in the neonatal period and then disappeared until adolescence in Stransky's case; at four, twelve and seventeen years in the others. One patient complained of pain in the upper right quadrant of the abdomen early in the course of his disease, whereas the other patients noted only intermittent fatiguability. Except for the presence of icterus, physical examination is within normal limits. The following laboratory studies are normal: complete blood count, erythrocyte morphology, reticulocyte count, thymol turbidity, zinc sulphate turbidity, concentration of total serum lipid and proteins, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, cholesterol and cholesterol esters. Serum alkaline phosphatase activity is 1 to 2.5 Bodansky units per 100 ml. Results of the cephalin cholesterol flocculation tests range from negative to 4 plus. The excretion of urobilinogen in the urine is normal or slightly elevated. Fecal urobilinogen excretion is within normal range. Serum bilirubin concentrations range from 5.3 to 17.7 mg. per cent and from approximately 30 to 70 per cent reacts directly with diazotized sulfanilic acid. Oral cholecystography is normal. Bromsulphalein retention forty-five minutes after the intravenous injection of 5 mg. of bromsulphalein per kg. of body weight ranges from 15 to 65 per cent. In the case studied by Schiff et al. [*5*], chromatographic examination of an alcoholic extract of the serum indicated that 45 to 50 per cent of the pigment existed as free bilirubin and 50 to 55 per cent as a conjugated pigment. The conjugated pigments consisted of 55 to 58 per cent as pigment I and from 42 to 45 per cent as pigment II. Thirty-four per cent of the direct-reacting bilirubin was found to be alkali-labile and 39 per cent was hydrolyzable by beta glucuronidase, which suggests that the major proportion of the conjugated pigment is in a form other than glucuronide [*5*]. Examination of serum obtained forty-five and ninety minutes after the intravenous injection of 5 mg. of bromsulphalein per kg. of body weight in two patients revealed that only 6 and 4 per cent of bromsulphalein in the serum was present as conjugated bromsulphalein at a time when the serum bromsulphalein retention was 57 and 36 per cent, respectively [*5*]. It was concluded that "since there is almost no regurgitation of metabolized bromsulphalein, biliary obstruction is unlikely and the elevated retention is due to an impairment in the produc-

tion of conjugated bromsulphalein [*5*]." Normal hepatic histology is observed in these cases.

Several clinical and chemical differences exist between these two syndromes. (1) An abnormal pigment is present in variable amounts in patients with the Dubin-Johnson syndrome. (2) There is a tendency for greater bromsulphalein retention in patients with the Rotor syndrome. (3) Bromsulphalein, which was retained in the plasma, was all in the unconjugated form in the patient described by Schiff et al. [*5*]. (4) Normal oral cholecystography is observed in patients without hepatic pigmentation. (5) An increased amount of non-glucuronide conjugated bilirubin was detected in the plasma of two patients with chronic idiopathic jaundice of the type described by Rotor [*5*]. (6) Urinary urobilinogen excretion is often slightly increased in patients with the Rotor syndrome, and serum alkaline phosphatase activity is often reduced. Many of these differences appear to be quantitative ones. Many of the investigations which have been conducted in patients with chronic idiopathic jaundice without hepatic pigmentation have not been performed in patients with the Dubin-Johnson syndrome.

In the present family study no significant clinical factors differentiate Case III from Cases I and II. Bromsulphalein retention in the serum was more marked in Case III and bromsulphalein conjugates accounted for most of the retained bromsulphalein at forty-five and 100 minutes. In each case, approximately 60 per cent of the direct-reacting bile pigments in plasma represented non-glucuronide conjugates of bilirubin. *In vivo* menthol tolerance tests and *in vitro* assays of hepatic glucuronyl transferase activity failed to demonstrate a defect in glucuronide formation.

Billing and Lathe [*26*] suggested that pigment I, which was identified in the siliconized kieselguhr columns of Cole and Lathe [*27*], is bilirubin monoglucuronide and that pigment II is bilirubin diglucuronide. Bollman et al. [*28*] have demonstrated that pigment I can be formed in extrahepatic sites. Pigment I has not unequivocally been demonstrated to be bilirubin monoglucuronide and may result from condensation of bilirubin and pigment II during the column chromatography [*26,29*]. Pigment I may be formed in the liver as part of an intermediate process in the formation of bilirubin diglucuronide. The presence of increased amounts of pigment I in the serum of patients with the Dubin-Johnson or Rotor syndromes need not indicate, as has been suggested [*5,6*], the existence of a defect in hepatic uptake of pigment I, but may result from interference with intracellular transport mechanisms.

The distribution of free and conjugated bromsulphalein in the serum of Case III differs from that observed by Grodsky [*16*] in the case of Schiff et al. [*5*]. Further studies of bromsulphalein conjugates in the serum of cases of chronic idiopathic jaundice with and without abnormal hepatic pigmentation are required in order to determine the significance and specificity of these observations.

Because of the normal relative hepatic storage of bromsulphalein in these patients, the markedly reduced hepatic Tm for bromsulphalein indicates that a defect exists in the process by which bromsulphalein is transported from the liver cell to the bile [*15*].

Histologic studies failed to demonstrate any abnormal pigment in four liver biopsy specimens in Case III. In liver specimens obtained from patients with the Dubin-Johnson syndrome, the abnormal pigment is uniformly distributed throughout [*1,23*]. It is, therefore, highly unlikely that further study of liver histology in Case III will reveal pigmentation which was fortuitously missed in four previous examinations. The pigment which is present in the Dubin-Johnson syndrome histochemically stains positively for acid phosphatase activity [*30*]. Other histochemical staining reactions are within normal limits.* These histochemical staining reactions were within normal limits in a liver biopsy specimen in Case III, with two exceptions: No staining reaction for alkaline phosphatase activity was demonstrable, and acid phosphatase staining reaction was abundant in close proximity to the bile canaliculi, particularly in the periportal areas of the liver.

Electron microscopic examination of a biopsy specimen of the liver was made in Cases I and III. The abnormalities in Case I have been previously described by Essner and Novikoff [*30*], who found the abnormal pigment in pericanalicular lysosomes. In Case III, electron microscopic examination did not reveal any pigmentation. Pericanalicular lysosmes were increased in numbers.

The rarity of the two syndromes makes it highly improbable that two unrelated defects are independently present in this family. The similarity in clinical and laboratory findings is consistent with the presence of a common func-

* See footnote on p. 512.

tional defect in these cases. The high familial incidence of chronic idiopathic jaundice with or without hepatic pigmentation suggests that these syndromes may result from inborn errors of metabolism. Hepatic glucuronyl transferase activity is normal and hence the etiologic mechanism differs from that observed in some patients with chronic unconjugated hyperbilirubinemia [*14,31*]. An alteration or defect in the poorly understood mechanisms by which conjugated bilirubin and other metabolites are excreted into the bile seems likely.

SUMMARY

Studies of three related patients with familial non-hemolytic jaundice with conjugated bilirubin in the serum are described. An unidentified pigment was present in the liver cells in two patients (Cases I and II) and a diagnosis of Dubin-Johnson syndrome was made. A liver specimen was obtained from the third patient (Case III) on four separate occasions and detailed histologic examination failed to reveal any abnormal intrahepatic pigmentation.

The survival of erythrocytes labelled with Cr^{51} was normal in the two patients in whom it was determined. Urinary and fecal urobilinogen excretion, menthol tolerance test and *in vitro* assay of hepatic glucuronyl transferase activity were within normal limits in all three cases. Determination of the distribution of bile pigments in the plasma, the relative amounts of dipyrrol azo pigments A and B after the addition of diazotized sulfanilic acid to serum, the percentage of dipyrrol azo pigment B which remained after alkaline and enzymatic hydrolysis, and the relative amounts of free and conjugated bromsulphalein in the serum forty-five and 100 minutes after the intravenous injection of 5 mg. bromsulphalein per kg. body weight were not significantly different in the three cases. The hepatic Tm for bromsulphalein was markedly reduced in all three cases. The relative hepatic storage of bromsulphalein was normal.

Histochemical studies revealed acid phosphatase-positive pericanalicular pigment granules in liver tissue obtained in Cases I and II. Four specimens of liver obtained in Case III did not reveal abnormal hepatic pigmentation. Histochemical study revealed increased pericanalicular acid phosphatase activity. On electron microscopic examination, abundant amounts of the abnormal pigment were seen in pericanalicular lysosomes in Case I.

The possibility is discussed that cases of chronic familial non-hemolytic jaundice with conjugated bilirubin in the serum with and without abnormal hepatic pigmentation may represent varied expressivity of a common functional defect in the poorly understood mechanisms by which bilirubin and other metabolites are transported from the liver cells into the bile.

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Ineffective Erythropoiesis*

FARID I. HAURANI, M.D. *and* L. M. TOCANTINS, M.D.
Philadelphia, Pennsylvania

THE term "ineffective erythropoiesis" (dysfunction of the bone marrow) was introduced [*1*] to describe hematologic disorders in which there is a discrepancy between the total red cell mass (or hemoglobin mass) in the peripheral circulation (effective erythropoiesis) and red cell production (and/or heme synthesis) in the bone marrow (total erythropoiesis) unexplained by blood loss alone (hemolysis or hemorrhage). In this state, although total erythropoiesis may be increased many times the normal, most of the synthesized heme seems to be destroyed *in situ* and is not destined to reach the peripheral circulation or else it survives very shortly (hours) in the peripheral circulation [*2*]. Such a situation exists whenever (1) the fecal urobilinogen is significantly increased despite a slightly altered red cell survival time (in this instance the increased fecal urobilinogen does not necessarily mean an increased destruction of circulating red cells), (2) there is an active erythroid hyperplasia of the bone marrow with a relatively low reticulocyte count in the peripheral circulation, (3) there is an increased plasma iron turnover with poor red cell utilization of iron.

In this paper will be reported the results of erythrokinetic studies (plasma iron turnover, red cell utilization, fecal urobilinogen, red cell survival, peripheral blood and bone marrow examination) in patients who manifested various degrees of ineffective erythropoiesis, compared with the results obtained in other diagnostically closely related patients in the same group. Limitations to the use of the indices in various types of anemia are also considered.

PATIENTS STUDIED

Hemoglobinopathies. There were twelve patients (ages fifteen to forty years) in this group, four with thalassemia, three with sickle cell-thalassemia, one with hemoglobin I-thalassemia, two with sickle cell disease and two with sickle cell-C disease. (Tables I and II.) The diagnosis of the abnormal hemoglobin in each of these patients was made on the basis of clinical, genetic and hematologic data including special biochemical and electrophoretic studies. The patient (Case VIII) with hemoglobin I-thalassemia had

TABLE I

HEMATOLOGIC DATA IN PATIENTS WITH THALASSEMIA AND ABNORMAL HEMOGLOBINS

Case No.	Diagnosis	Reticulocyte Count (%)	Red Blood Cells (in millions)	Mean Corpuscular Hemoglobin Concentration (%)	Actual Hemoglobin Mass (gm.)	Expected Hemoglobin Mass (gm.)	Serum Iron (μg. %)	Total Iron Binding Capacity (μg. %)	Fe^{59} T/2 Clearance (min.)	Maximum Utilization of Fe^{59} (%)	Fecal Urobilinogen (mg./day)	Mean Cell Life Days (Cr^{51})	Bone Marrow Nucleated Red Blood Cells/1,000 Myeloid Cells
I	Thalassemia	5	4.4	25.5	229	391	95	170	14	33	430	35	3,010
II	Thalassemia	6.2	3.28	26	267	437	147	317	40	35	573.5	42	2,350
III	Thalassemia	8	3.46	30	393	513	214	264	18	33	...	38.5	3,100
IV	Thalassemia	1.7	4.4	22.6	346	630	270	270	36	22	215	120	1,840
V	Sickle cell-thalassemia	2	3.7	30	315	418	94	214	41	79	139	...	...
VI	Sickle cell-thalassemia	9	3.78	24.4	332	546	105	...	25	85	295	26	...
VII	Sickle cell-thalassemia	5.2	2.43	30	243	471	175	300	40	60	396	32	1,250
VIII	I-thalassemia	2	3.66	30	478	600	85	435	24	94	...	120	488
IX	Sickle cell	14.6	2.11	32.6	212	487	168	250	30	57	3,216	14	2,315
X	Sickle cell	12.5	3.6	32	460	675	268	429	23	95	1,297	16	...
XI	Sickle cell-C	2.7	4.1	30	545	572	64	344	44	82	189	75	1,500
XII	Sickle cell-C	2.8	4.24	31	479	582.4	41	291	43	92	214	100	900
Normal		1.0	4.5–5	32–36	...	...	50–150	270–400	60–120	>75	100–250	120	463

* From the Charlotte Drake Cardeza Foundation, Jefferson Medical College, Philadelphia, Pennsylvania. Manuscript received December 23, 1960.

TABLE II

ERYTHROPOIESIS PRODUCTION INDICES IN PATIENTS WITH THALASSEMIA MAJOR (CASES I THROUGH IV) AND ABNORMAL HEMOGLOBIN (CASES V THROUGH XII) (A NORMAL INDEX IS UNITY)

Case No.	Diagnosis	Total Erythropoiesis				Effective Erythropoiesis				Bone Marrow Efficiency (%)
		Bone Marrow	Plasma Iron Turnover	Fecal Urobilinogen	Average	Reticulocytes	Fe^{59} Utilization	Cr^{51} Survival	Average	
I	Thalassemia	6.5	5.8	5	5.8	3.7	3	3.4	3.3	57
II	Thalassemia	5.1	5.4	6	5.5	3.4	4	2.1	3.2	58
III	Thalassemia	7	9.5	...	8.2	5.4	4.1	2.4	4	50
IV	Thalassemia	4	5.8	...	4.9	1	1.04	0.54	0.8	16
V	Sickle cell-thalassemia	...	2.5	1.5	2	1.4	2	...	1.7	85
VI	Sickle cell-thalassemia	...	4	2.5	3.3	5.3	3.4	2.7	3.8	100
VII	Sickle cell-thalassemia	2.7	4.8	3.8	3.8	2.5	3.5	1.8	2.6	68
VIII	I-thalassemia	1.1	1.4	...	1.3	1.6	1.3	0.8	1.2	92
IX	Sickle cell	5.0	4.8	6.6	5.5	6.8	3.6	4	4.8	87
X	Sickle cell	...	9	9	9	9	8.5	7	8.3	92
XI	Sickle cell-C	2.5	1.9	1.5	2	2	1.6	1.2	1.6	80
XII	Sickle cell-C	2	1	1.6	1.5	2.5	0.9	1	1.4	93

TABLE III

HEMATOLOGIC DATA IN TEN PATIENTS WITH MYELOSCLEROSIS AND EXTRAMEDULLARY HEMOPOIESIS (CASES I THROUGH X) AND TWO PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA (CASES XI AND XII)

Case No.	Diagnosis	Reticulocyte Count (%)	Red Blood Cells (in millions)	Mean Corpuscular Hemoglobin Concentration (%)	White Blood Cells (thousands)	Normoblasts/100 White Blood Cells	Actual Hemoglobin Mass (gm.)	Expected Hemoglobin Mass (gm.)	Serum Iron (μg. %)	Total Iron Binding Capacity (μg. %)	Fe^{59} T/2 Clearance (min.)	Maximum Utilization of Fe^{59} (%)	Fecal Urobilinogen (mg./day)	Mean Cell Life Days (Cr^{51})	Bone Marrow Nucleated Red Blood Cells/1,000 Myeloid Cells
I	Myelosclerosis	4.7	3.58	29.4	12.2	1	550	825	165	...	135	51	...	...	230
II	Myelosclerosis (before splenectomy)	0.7	2.6	36.8	4.7	Rare	283	525	225	275	40	6	399	26	0
II	Myelosclerosis (after splenectomy)	3	3.42	30	13.8	4.5	355	525	109	109	125	15	215	120	0
III	Myelosclerosis	5.6	2.0	28.5	5.5	Rare	410	948	76	201	35	17	960	35	0
IV	Myelosclerosis (before splenectomy)	6.9	1.96	33.5	4.6	Rare	270	683	67	67	46	27.5	767	32	0
IV	Myelosclerosis (after splenectomy)	1.9	2.49	31	18 5	54	265	683	78	228	150	20	174	100	0
V	Myelosclerosis	3.2	2.63	40	4.5	9	400	812	180	230	146	33	345	32	0
VI	Myelosclerosis (before splenectomy)	4.6	2.02	22.2	10.5	4	212	679	87	247	27	35	1,355	29	0
VI	Myelosclerosis (after splenectomy)	3.5	3.31	32.2	12.35	4	396	653	71	221	126	24	313	93	0
VII	Myelosclerosis	4.9	3.5	29.8	78.5	11	592	750	75	355	48	58	455	120	0
VIII	Myelosclerosis	5	6.2	24.5	108	14	608	402	26	353	9	74	239	120	0
IX	Myelosclerosis	1.2	2.51	30.9	3.2	1	430	735	86	186	97	27	...	35	0
X	Myelosclerosis	1	2.34	27.2	8 5	3	311	735	61	361	76	47	549	46	0
XI	Chronic myeloid leukemia	5.7	2.62	29	68 5	0	423	825	48	298	20	76	142	42	<50
XII	Chronic myeloid leukemia	6.4	3.12	36	287	1	497	735	143	...	60	60	10	46	<50
Normal		1	4.5–5	32–36	8–10	None	...	...	50–150	270–400	60–120	>75	100–250	120	463

70 per cent hemoglobin I and 30 per cent hemoglobin A by paper electrophoresis [*3*]. The diagnosis of sickle cell-thalassemia could not be confirmed in one patient (Case VII) by electrophoretic or genetic studies although the rest of the studies favored such a diagnosis. All patients were in clinical remission (production and destruction of red blood cells in equilibrium) at the time of study, and none had required transfusions within the preceding year, except for two (Cases V and VI) three and four months, respectively. Two patients (Cases II and V) with a thalassemic defect had had splenectomy for an extracorpuscular defect [*4*] and the studies reported herein were made one year and one month after splenectomy, respectively.

Myelosclerosis and Extramedullary Hemopoiesis Group. This group consisted of twelve patients. (Tables III

TABLE IV

ERYTHROPOIESIS PRODUCTION INDICES IN TEN PATIENTS WITH MYELOSCLEROSIS AND EXTRAMEDULLARY HEMOPOIESIS (CASES I THROUGH X) AND TWO PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA (CASES XI AND XII) (A NORMAL INDEX IS UNITY)

Case No.	Diagnosis	Total Erythropoiesis			Effective Erythropoiesis			Bone Marrow Efficiency (%)
		Bone Marrow	Plasma Iron Turnover	Fecal Urolibilinogen	Reticulocytes	Fe^{59} Utilization	Cr^{51} Survival	
I	Myelosclerosis	0.5	0.9	...	2.9	0.6	...	66
II	Myelosclerosis (before splenectomy)	...	4.8	3.5	0.36	0.38	2.4	9
II	Myelosclerosis (after splenectomy)	...	0.66	1.9	2.0	0.13	0.68	...
III	Myelosclerosis	...	2.1	4.6	1.9	0.5	1.0	21
IV	Myelosclerosis (before splenectomy)	...	2.0	5.0	2.7	0.7	1.5	30
IV	Myelosclerosis (after splenectomy)	...	0.4	1.3	0.95	0.1	0.6	...
V	Myelosclerosis	...	0.83	1.9	1.8	0.4	2.2	...
VI	Myelosclerosis (before splenectomy)	...	2.0	9.0	1.3	1.0	1.2	...
VI	Myelosclerosis (after splenectomy)	...	0.3	2.0	2.6	0.1	0.6	...
VII	Myelosclerosis	...	1.5	2.7	3.0	1.4	0.6	22
VIII	Myelosclerosis	...	1.8	2.7	4.8	1.8	0.7	...
IX	Myelosclerosis	...	1.0	...	0.54	0.4	1.5	47
X	Myelosclerosis	...	0.6	3.4	0.4	0.4	0.96	...
XI	Chronic myeloid leukemia	<0.1	1.7	0.78	2.6	1.3	1.3	100
XII	Chronic myeloid leukemia	<0.1	2	...	4	1.7	1.6	100

TABLE V

HEMATOLOGIC DATA IN PATIENTS WITH APLASTIC ANEMIA (CASES I THROUGH V) AND REFRACTORY NORMOBLASTIC ANEMIA (CASES VI AND VII)

Case No.	Diagnosis	Reticulocyte Count (%)	Red Blood Cells (in millions)	Mean Corpuscular Hemoglobin Concentration (%)	Actual Hemoglobin Mass (gm.)	Expected Hemoglobin Mass (gm.)	Serum Iron (μg. %)	Total Iron Binding Capacity (μg. %)	Fe^{59} T/2 Clearance (min.)	Maximum Utilization of Fe^{59} (%)	Fecal Urobilinogen (mg./day)	Mean Cell Life Days (Cr^{51})	Bone Marrow Nucleated Red Blood Cells/1,000 Myeloid Cells
I	Aplastic anemia	<0.1	1.9	30	308	840	275	345	>480	8	244	88	<50
II	Aplastic anemia	0 8	3.38	33.9	488	675	137	277	>600	30	...	...	<50
III	Aplastic anemia	0.2	2.5	36	488	840	171	171	252	40	70	...	<50
IV	Aplastic anemia	0.1	1.62	26.4	210	471	149	224	>600	0	...	38.5	<50
V	Aplastic anemia	3.4	2.55	33	333.5	840	262	322	275	28	86	42	<50
VI	Refractory normoblastic anemia	2.5	3.25	33	530	780	103	203	16	31	611	88	2,350
VII	Refractory normoblastic anemia	1	2.45	32.7	436	735	361	361	72	14	812	21	1,900
Normal		1	4.5–5	32–36	...	...	50–150	270–400	60–120	>75	100–250	120	463

TABLE VI

ERYTHROPOIESIS PRODUCTION INDICES IN PATIENTS WITH APLASTIC ANEMIA (CASES I THROUGH V) AND REFRACTORY NORMOBLASTIC ANEMIA (CASES VI AND VII) (A NORMAL INDEX IS UNITY)

Case No.	Diagnosis	Total Erythropoiesis			Effective Erythropoiesis			Bone Marrow Efficiency (%)
		Bone Marrow	Plasma Iron Turnover	Fecal Urobilinogen	Reticulocytes	Fe^{59} Utilization	Cr^{51} Survival	
I	Aplastic anemia	<0.1	<0.1	1.3	<0.1	<0.1	0.56	...
II	Aplastic anemia	<0.1	<0.1	...	0.5	<0.1	...	...
III	Aplastic anemia	<0.1	0.4	0.36	<0.1	0.33	...	...
IV	Aplastic anemia	<0.1	<0.1	...	<0.1	<0.1	1.1	...
V	Aplastic anemia	<0.1	0.6	0.5	1.7	0.25	1.4	...
VI	Refractory normoblastic anemia	5	5	3.6	1.6	1.8	0.9	31
VII	Refractory normoblastic anemia	4	4.4	5	0.5	0.8	2.8	15

TABLE VII

HEMATOLOGIC DATA IN PATIENTS IN GROUP IV (MISCELLANEOUS)*

Case No.	Diagnosis	Reticulocyte Count (%)	Red Blood Cells (in millions)	Mean Corpuscular Hemoglobin Concentration (%)	Actual Hemoglobin Mass (gm.)	Expected Hemoglobin Mass (gm.)	Serum Iron (μg. %)	Total Iron Binding Capacity (μg. %)	Fe^{59} T/2 Clearance (min.)	Maximum Utilization of Fe^{59} (%)	Fecal Urobilinogen (mg./day)	Mean Cell Life Days (Cr^{51})	Bone Marrow Nucleated Red Blood Cells/1,000 Myeloid Cells
I	Hemochromatosis	0.9	4.28	32	690	787.5	223	323	145	47	223	107	470
II	Hemochromatosis	1.8	3.47	31	399	435	278	353	84	50	54	120	510
II	Hemochromatosis	1.5	3.88	35	406	435	232	232	90	64	...	100	...
III	Megaloblastic anemia	1.1	1.1	32	124	578	230	230	70	8.5	...	42	1,410
IV	Acute Di Guglielmo's disease	20.1	2.7	27	78.3	145	...	...	...	...	87	120	5,550
V	Polycythemia vera	2	6.59	27	749	435	53	...	26	95	215	...	*
VI	Hypersplenism (before splenectomy)	3	2.97	29.1	450	653	108	175	43	58	447	75	<50
VI	Hypersplenism (after splenectomy)	8.4	4.14	...	588	653	...	...	36	85	...	...	<50
Normal		1	4.5–5	32–36	...	...	50–150	270–400	60–120	>75	100–250	120	463

* Bone marrow examination is not representative.

TABLE VIII

ERYTHROPOIESIS PRODUCTION INDICES OF PATIENTS IN GROUP IV (A NORMAL INDEX IS UNITY)*

Case No.	Diagnosis	Total Erythropoiesis			Effective Erythropoiesis			Bone Marrow Efficiency (%)
		Bone Marrow	Plasma Iron Turnover	Fecal Urobilinogen	Reticulocytes	Fe^{59} Utilization	Cr^{51} Survival	
I	Hemochromatosis	1	0.8	1.3	0.8	0.5	0.9	...
II	Hemochromatosis	1.1	2.5	0.6	1.4	1.7	0.8	...
II	Hemochromatosis	...	2.5	...	1.3	2	1	...
III	Megaloblastic anemia	3	3	...	0.24	0.32	0.57	13
IV	Acute Di Guglielmo syndrome	12	...	3	16	...	0.5	...
V	Polycythemia vera	*	1.2	2.2	3	1.5	...	100
VI	Hypersplenism (before splenectomy)	0.1	2	3	2	1.6	1.1	...
VI	Hypersplenism (after splenectomy)	0.1	2	...	7.7	1.7	...	...

* Bone marrow aspiration not representative.

and IV.) Ten patients had extramedullary hemopoiesis; in nine myelosclerosis of the bone marrow was demonstrated by bone biopsies and in one (Case V) a malignant lymphoma was present. In most, the diagnosis was further confirmed by liver and/or spleen biopsies. There were three women (Cases V, VI and VIII), one of whom (Case VIII) presented herself two years after she had undergone splenectomy, at which time an enlarged liver was found to occupy most of the abdominal cavity. Three patients (Cases II, IV and VI) underwent splenectomy, and erythrokinetic studies were performed before and from one to six months after the operation. Two patients (Cases XI and XII) had chronic myelogenous leukemia.

Refractory Normoblastic Anemia Group. This group (Tables V and VI) consisted of seven patients, two of whom (Cases VI and VII) had refractory normoblastic anemia; the rest had aplastic anemia.

Miscellaneous Group. This group (Tables VII and VIII) consisted of five patients, two of whom (Cases I and II) had primary hemochromatosis. The diagnosis was confirmed by liver biopsies and by the fact that despite several phlebotomies there was no decrease in the hemoglobin concentration or serum iron level. One patient (Case III) had a megaloblastic anemia due to malabsorption of vitamin B_{12} and responded well to therapy with the vitamin. Another (Case V) had polycythemia vera. One patient (Case IV), a three year old girl, had acute di Guglielmo disease. The last patient of the group had pancytopenia probably due to hypersplenism.

METHODS

Differential counts on bone marrow cells were performed on erythrocytic cells encountered on counting 200 myelocytic cells and the final count was expressed per 1,000 myeloid cells (excluding lymphocytes, monocytes, plasma cells and reticulum cells). Fecal urobilinogen was measured according to the method of Watson [5]. Serum iron was measured by a modification of the method of Peterson [6], using 4,7-diphenyl-1,10-phenanthroline. Blood volume was determined by the Cr^{51}-tagged red cell method.

Survival of Cr^{51}-labeled red cells was determined

by the method of Read et al. [7]. Thirty milliliters of the patient's blood was incubated with 100 μc. of Cr^{51} (as Na_2CrO_4) in a 100 ml. sterile siliconized bottle containing 10 ml. of ACD solution for forty-five minutes at room temperature. Tagging was stopped with 100 mg. of vitamin C. The first sample was taken fifteen minutes after injection of the Cr^{51}-tagged red blood cells for the determination of blood volume, the second was taken twenty-four hours later in most instances. Three or four samples were collected subsequently over a two-week period. The red cell apparent half-life (T/2 Cr^{51}) was determined by plotting the counts of the collected specimen on semi-logarithmic paper and extrapolating to zero time. The day on which 50 per cent of the activity was present was the T/2 Cr^{51}. In sixty-six experiments the extrapolated zero point coincided with the determined zero point (less than 5 per cent difference) in 76 per cent of the determinations. Large spleens did not seem to influence the difference, but a severe hemolytic process was present in every instance in which the difference was more than 5 per cent. The mean red cell life (MCL) was calculated from the T/2 Cr^{51} values as described by Donohue et al. [8] but when the T/2 Cr^{51} value was above twenty days the conversion table of Engstedt [9] was used.

The plasma iron turnover and red cell utilization were measured according to the method of Huff [10]. In most patients, radioiron was diluted with saline solution without incubation with plasma and injected immediately after the collection of the Cr^{51} fifteen-minute sample. There was no difference in the plasma iron turnover whether the Fe^{59} was incubated with plasma or not [11–13]. In patients in whom the serum iron-binding protein is almost or completely saturated, doubt has risen whether the red cell utilization data could be reliable if the radioiron is not incubated with plasma prior to injection [12]. In one patient (Case IV, Table III) with completely saturated plasma-binding capacity, Fe^{59} utilization was 27.5 per cent without incubation of radioiron with plasma and 20 per cent with incubation.

The production indices were employed to express the rate of blood production in comparison to normal. The indices were obtained by the formulas given by Giblett et al. [1] and the normal standards used in the calculations were those given by the authors, since they did not differ significantly from normal values obtained in this laboratory. In these formulas, production was calculated by relating the patient's data to the expected hemoglobin mass, destruction was related to the actual hemoglobin mass. Indices that usually express red cell production were converted to express hemoglobin production by multiplying the indices by the ratio of the actual mean corpuscular hemoglobin concentration to normal. The specific formulas are:

(1) Reticulocyte index:

$$\text{Reticulocytes per cent} \times \frac{\text{Patient red cell count}}{\text{Normal red cell count}}$$

(where normal red cell count = 5 million/cu. mm. for males and 4.5 million/cu. mm. for females)

(2) Cr^{51}survival index:

$$\frac{120}{\text{Patient red cell survival (MCL)}} \times \frac{\text{Patient red cell count}}{\text{Normal red cell count}}$$

(3) Red cell utilization index:

$$\frac{\text{Plasma iron turnover mg./day} \times \text{maximum utilization per cent}}{\text{Normal hemoglobin mass (gm.)}}$$

(4) Plasma iron turnover index:

$$\frac{\text{Plasma iron turnover (mg./day)}}{\text{Normal hemoglobin mass (gm.)}}$$

(5) Fecal urobilinogen index:

$$\frac{\text{Fecal urobilinogen/day (mg.)}}{\text{Normal hemoglobin mass (gm.)}}$$

(6) Bone marrow index:

$$\frac{\text{Nucleated red blood cells/1,000 myeloid cells}}{\text{463 (normal)}}$$

Of the six indices mentioned, the reticulocyte, red cell utilization and Cr^{51} survival represent effective erythropoiesis whereas the rest represent total erythropoiesis. For a given case, the efficiency of the bone marrow (or effective erythropoiesis) was obtained when possible, as follows:

Effective erythropoiesis (per cent):

$$\frac{\text{Average of effective erythropoiesis indices}}{\text{Average of total erythropoiesis indices}} \times 100$$

In three patients with myelosclerosis and extramedullary hemopoiesis, and four other patients, the uptake of radioiron by the spleen was measured *in vitro* after removal of the spleen. (Table IX.) The radioactive iron material was injected intravenously from two hours to three days before splenectomy. The radioiron T/2 clearance rate and the utilization of radioiron were determined before and after splenectomy, respectively. Half of the spleen (cut longitudinally) was homogenized and the radioactivity of a sample was determined. (The radioactivity of the counted sample was usually more than twenty times the background.)

TABLE IX
UPTAKE OF RADIOIRON BY THE SPLEEN (IN PERCENTAGE)

Diagnosis	Weight (gm.) and Pathology of Spleen	Hours Fe^{59} Injected Before Splenectomy	Uptake of Fe^{59} by Spleen (%)	Fe^{59} T/2 (min.)	Fe^{59} Maximum Utilization (%)
Myelosclerosis	1,140; Extramedullary hemopoiesis	2	3.6	...	...
Congenital spherocytic anemia	480; Congestion	2	0.4	...	77
Myelosclerosis	730; Extramedullary hemopoiesis	4	1.2	135	51
Malignant lymphoma	2,000; Lymphocytic infiltration	15	4.4	70	84
Acquired hemolytic anemia	1,285; Congestion	16	19	30	85
Myelosclerosis pancytopenia	1,450; Congestion	72	5	36	85
Mycosis fungoides	1,900	20	6.6	78	93

In six patients who underwent splenectomy, blood volume determinations were performed before and after splenectomy. (Table X.)

ANALYSIS OF RESULTS AND COMMENTS

Group 1. Hemoglobinopathies. Thalassemia major, which strictly speaking may not be a hemoglobinopathy [*14*], was included to provide a basis for comparison. The erythrokinetic studies in this group revealed ineffective erythropoiesis or dysfunction of the bone marrow only in patients with thalassemia major. In three patients with sickle cell-thalassemia and one patient with hemoglobin I-thalassemia a decrease in effective erythropoiesis could not be demonstrated, with the possible exception of one patient (Case VII).

Figure 1 depicts the Fe^{59} utilization curves. In the patients with thalassemia the Fe^{59} utilization was low (22 to 33 per cent) as compared to the values obtained in other patients. Table I depicts the hematologic data from which the erythropoiesis production indices (Table II) were calculated. The average total erythropoiesis (5.8, 5.5, 8.2, 4.9) in the group with thalassemia was about six times normal, while the average effective erythropoiesis (3.3, 3.2, 4, 0.8) was about three times normal. The average efficiency of the bone marrow was 50 per cent. This is to say that of all the hemoglobin which the bone marrow produced, only half was delivered effectively to the peripheral circulation. In three patients, the mean cell life of the red blood cells was shortened (35, 42, 38.5 days) and this accelerated destruction of circulating red cells could account partly for the anemia. However, in one patient (Case IV) the anemia must have been entirely due to ineffective erythropoiesis (dysfunction of the bone marrow) since the mean red cell life was normal (120 days).

TABLE X
BLOOD VOLUME DETERMINATIONS IN SIX PATIENTS BEFORE AND AFTER SPLENECTOMY

Diagnosis	Weight of Spleen (gm.)	Blood Volume (ml.)	
		Before Splenectomy	After Splenectomy
Myelosclerosis	835	3,500	3,700
Myelosclerosis	1,140	3,500	3,600
Myelosclerosis	1,390	4,100	3,840
Thalassemia	690	4,600	4,180
Sickle cell-thalassemia	1,000	3,500	4,100
Hemolytic anemia	1,450	4,150	4,160

In sickle cell disease the mechanism of the anemia was due entirely to incomplete compensation of the bone marrow to the increased rate of hemolysis. The production indices were highest (5.5 and 9 times normal) and the red cell survival was shortest (mean cell life: fourteen and sixteen days). The efficiency of the bone marrow was approximately 90 per cent of normal. The three patients with sickle cell-thalassemia behaved erythrokinetically similar to the patients with sickle cell disease. There was no evidence of dysfunction of erythropoiesis. The hemolytic process was milder than in sickle cell disease (mean cell life: twenty-six and thirty-two days) but more severe than in thalassemia and

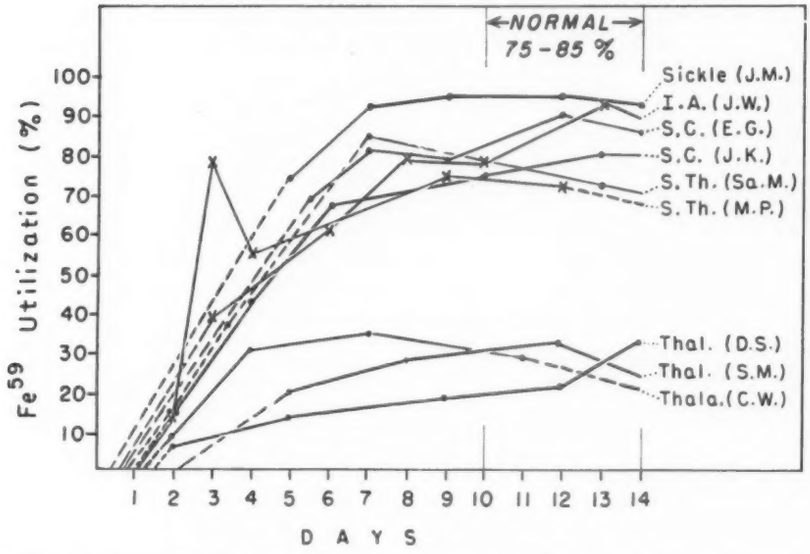


FIG. 1. Radioiron utilization curves in patients with thalassemia and abnormal hemoglobin disorders.

sickle cell-C disease, in which the mean cell life was seventy-five and one hundred days. The bone marrow was capable of compensating at approximately three times the normal rate in sickle cell-thalassemia and 1.75 times normal in sickle cell-C disease to correct for the anemia. In hemoglobin C disease and sickle cell-D disease, erythrokinetic studies have also demonstrated normal effective erythropoiesis [*15,16*]. The patient with I-thalassemia had very mild anemia with normal survival of the red cells.

Of special interest in this group is the fact that the thalassemia disorders combined with hemoglobin S or hemoglobin I behaved erythrokinetically more like the corresponding hemoglobinopathies than like thalassemia. In all the patients studied the percentage of abnormal hemoglobin was more than 50 per cent. We have had no opportunity to study a patient with a combined thalassemia disorder with less than 50 per cent of abnormal hemoglobin. This type of patient may be expected to behave like one with thalassemia erythrokinetically. Ingram [*17*] postulates that the more common combination (i.e., that with a high percentage of abnormal hemoglobin) is due to the presence of the abnormal hemoglobin gene and the thalassemia gene on the same hemoglobin chain gene. In the case of sickle cell-thalassemia disease, the "S" gene and thalassemia gene are on the hemoglobin beta chain gene, one beta chain gene producing hemoglobin at a slow rate. Thus it would be expected that the ratio of hemoglobin S to hemoglobin A in sickle cell-thalassemia would be higher than in the case of sickle cell trait.

The question whether thalassemia is a hemoglobinopathy or not has not been settled. Ingram [*17*] believes, on the basis of genetic studies, that the hemoglobin of thalassemia has an abnormal globin moiety, although electrophoretically it has the same mobility as hemoglobin A. The abnormality is postulated to be due to "hidden" substitution of perhaps not more than one single amino acid residue by a new one (as in hemoglobins S, C, D and E) and that this abnormality accounts for the slow rate of "thalassemic" hemoglobin synthesis. On the other hand, there is evidence to incriminate the heme moiety as responsible for the thalassemic defect. Bannerman et al. [*18*] have suggested a partial block in the combination of protoporphyrin and iron in thalassemia. The conclusion was based on the observation that free erythrocyte protoporphyrin was normal or increased [*19*] and incorporation of 2-C^{14} glycine into protoporphyrin was brisk, whereas the incorporation of Fe^{59} into heme was poor, but was accelerated by the addition of protoporphyrin. The demonstration of ineffective erythropoiesis in thalassemia indicates that the total hemoglobin synthesis of the bone marrow is increased, even though only a fraction is delivered to the peripheral circulation [*20–22*]. Erythrokinetically, thalassemia seems to be different from the other hemoglobinopathies. Also, there is a close resemblance between thalassemia

and another disease in which the biosynthesis of heme is defective. A deficiency of pyridoxine [*23,24*] is characterized by hypochromic anemia, normal or elevated serum iron, normal hemoglobin by electrophoresis and a discrepancy between plasma iron turnover and red cell iron utilization. Pyridoxine is essential to the activation of glycine in the first step of heme synthesis [*25*].

Group 2. Myelosclerosis and Extramedullary Hemopoiesis. This group, consisting of ten patients with extramedullary hemopoiesis and two patients with chronic myelogenous leukemia (Tables III and IV), showed a number of discrepancies in the production indices, so that the bone marrow functional efficiency could not be determined for each case. In most patients the reticulocyte production index was elevated above the other indices of effective erythropoiesis. This may have been the result of poor control over the release of cells from the foci of extramedullary hemopoiesis and/or delayed structural maturation of these cells. In one patient the radioiron uptake of reticulocytes *in vitro* was less than expected. For these reasons the reticulocyte count seems to be a poor index of effective erythropoiesis in patients with extramedullary hematopoiesis.

In a few patients (Cases II, V and IX) who had received blood transfusions within a period of one month prior to the performance of these tests, the Cr^{51} survival was elevated, not in keeping with other indices. It seems that when total erythropoiesis is incapable of responding to an increased demand incurred by hemolysis, and this failure is corrected by blood transfusion, the Cr^{51} survival production index is a poor measure of effective erythropoiesis.

Another interesting finding, especially in patients who had previously had no blood transfusions, was the discrepancy between plasma iron turnover production index and the fecal urobilinogen index as measurements of total erythropoiesis. In every determination the fecal urobilinogen production index was higher than the plasma iron turnover production index (Cases II, III, IV, VI and X). The plasma iron turnover production indices seemed to vary from a value less than normal to a value almost twice normal, whereas the fecal urobilinogen production indices were two to three times higher (except in Cases VI and X). One observation that could account for this discrepancy is that the group as a whole had a low normal level of serum iron. In all patients who had a significant discrepancy between the plasma iron turnover production index and the fecal urobilinogen index, the level of serum iron was less than 90 μg./100 ml. even though no blood loss or malnutrition was demonstrated in any. In one patient (Case VIII) who had slight erythrocytosis the serum iron was very low (26 μg./100 ml.) and the red cells were hypochromic (mean corpuscular hemoglobin concentration was 24.5 per cent). This is in contrast to the patients with aplastic anemia or refractory normoblastic anemia, in whom the levels of serum iron were strikingly elevated. (Table V.)

Despite the shortcomings of these indices, some conclusions can be drawn as to their significance in extramedullary erythropoiesis. The total erythropoiesis of these extramedullary foci is not remarkably higher than normal as compared to thalassemia, sickle cell anemia or megaloblastic anemia. Ineffective erythropoiesis does occur in these extramedullary foci. There is a discrepancy between the plasma iron clearance and uptake of iron by the red cells in all patients except one (Case VIII) in whom a concomitant hypoferremia might have been responsible for normal Fe^{59} utilization. Also there is a discrepancy between the fecal urobilinogen destruction index (hemolytic index) and the red cell survival as determined by the Cr^{51} method. It therefore seems that in extramedullary hemopoiesis, as in pernicious anemia and thalassemia, only a portion of the formed hemoglobin reaches the peripheral circulation. It is of interest that in all these conditions the red cells are characterized by poikilocytosis and anisocytosis [*26–28*]. In at least two of four patients with myelosclerosis and extramedullary hemopoiesis, Nathan and Berlin [*27*] presented data suggesting a similar pattern of dysfunction of erythropoiesis.

In determining erythrokinetic indices from the hematologic data it is important to know whether the presence of a very large spleen in extramedullary hemopoiesis, or any large spleen for that matter, could influence (1) the plasma radioiron clearance rate *directly*, and more importantly the red cell utilization of radioiron, and (2) the patient's blood volume. In seven patients (Table IX) the uptake by the spleen of intravenously injected radioiron prior to splenectomy was determined *in vitro* after removal of the spleen. The weight of the spleens varied from 480 to 2,000 gm. (average 1,312 gm.). The uptake of radioiron by the spleen was low in all

except one patient who had acquired hemolytic anemia and in whom the Fe^{59} splenic uptake was 19 per cent. Since no correction was made for the radioiron in the newly formed red blood cells circulating in the spleen, the uptake of iron by splenic tissue must be lower than the values given in the table. However, these values are not high enough to suggest that a large spleen influences significantly red cell utilization of radioiron and directly the rate of plasma Fe^{59} clearance.

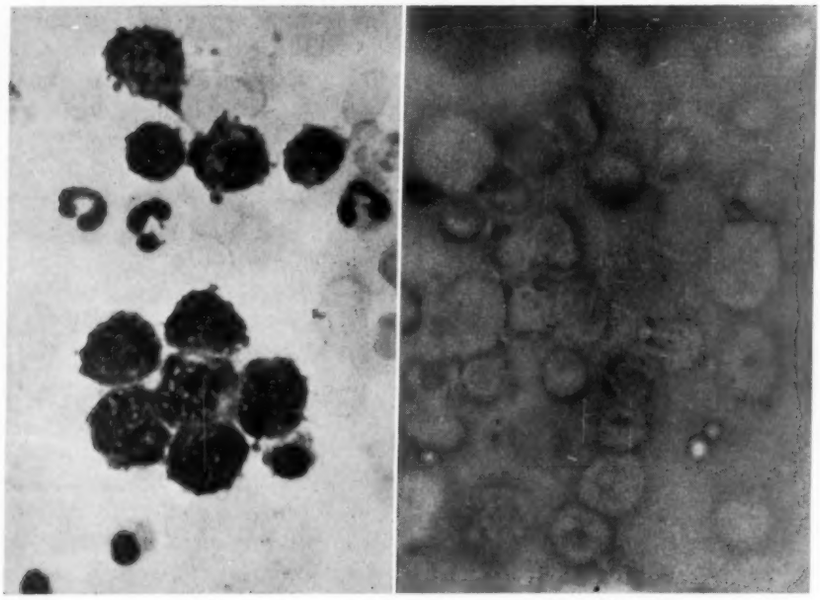
Two patients of this group had myelosclerosis with extramedullary hemopoiesis and the uptake of radioiron by the spleen was, to our surprise, low (3.6 and 1.2 per cent). This observation is in contradiction to the observed *in vivo* studies [*27,29*] and the prevailing concept that there is active erythropoiesis in the spleen in this disorder. On the basis of this study it seems more likely that the spleen acts only as a filter and graveyard to immature erythroid cells. This is borne out by the low uptake of radioiron by the spleen and by the fact that splenectomy in this condition has not led to disastrous effects [*30,31*]; in our series it has actually been beneficial. The leukoerythroblastic counts of the peripheral blood increased from low to high levels after splenectomy. (Table III.) In three patients with extramedullary hemopoiesis in whom erythrokinetic studies were made before and after splenectomy there was no significant change in the utilization of radioiron. There was a significant difference in the clearance of radioiron from the peripheral circulation but this could not be due to direct clearance by the spleen because the uptake of iron by the removed spleen, when measured *in vitro*, was low.

The other variable that may influence the validity of the production index is the blood volume. It has been suggested that huge spleens may act as reservoirs of blood and interfere with the accurate estimation of blood volume. In six patients (Table X) who underwent splenectomy the blood volume was determined prior to and after (one to six months) the operation. In three the blood volume was determined by the Cr^{51} technic and there was no significant change in the blood volume determination before and after splenectomy. In the other three the determinations were performed by the Fe^{59} method. There was a decrease of 9 per cent in one, an increase of 17 per cent in another, and no change in the third.

In two patients with chronic myelogenous leukemia, ineffective erythropoiesis was not demonstrated. The anemia seems to be secondary to a relative failure of the bone marrow, which appears to be incapable of compensating for the increased hemolysis. The hemolytic process has been ascribed to an intrinsic defect in the red blood cells [*32*]. The bone marrow index is misleading and suggests an absolute erythroid hypoplasia due to replacement by myeloid tissue.

Group 3. Refractory Normoblastic Anemia. This group consisted of seven patients. Five had aplastic anemia and two had refractory normoblastic anemia. The hematologic data are presented in Table V and the production indices in Table VI. The serum iron level was elevated in all patients and in two (Cases III and VII) the iron-binding protein was saturated. The mean corpuscular hemoglobin concentration was almost normal in the two patients with refractory normoblastic anemia. However, peripheral blood smears from these two patients showed a moderate degree of hypochromia, not uniformly present. The bone marrow was hypocellular, as expected in patients with aplastic anemia, and extremely cellular, especially in erythroid precursors, in refractory normoblastic anemia. The increased red cell precursors, the polychromatic and orthochromatic normoblasts, demonstrated an increased amount of iron pigment almost forming a collar around the nucleus. (Fig. 2.) The plasma radioiron clearance rate was slow and the utilization of iron poor in all patients with aplastic anemia, whereas in patients with refractory normoblastic anemia the plasma radioiron clearance rate was rapid but the utilization of radioiron by red cells was poor. The Cr^{51} red cell survival was shortened slightly in one patient (Case VI) with refractory normoblastic anemia and moderately in the other (Case VII). However, in both the daily excretion of fecal urobilinogen was increased above what was expected from the Cr^{51} red cell survival determinations. This is better illustrated in the patient (Case VI) in whom the destruction rate of the red cells, as determined by Cr^{51} method, was 1.36 of normal and almost ten times normal as determined from fecal urobilinogen (hemolytic index).

In examining the production indices given in Table VI one observes that the Cr^{51} survival production index, and occasionally the fecal urobilinogen production index, is not in keeping with other indices (Cases I, IV, V and VII). Since



2A 2B

FIG. 2. Refractory normoblastic anemia. A, increased erythropoiesis. B, excessive iron pigments in the cytoplasm of red cell precursors. Iron stain.

in these patients the determinations were performed after blood transfusions were given, the indices would be measuring both endogenous and exogenous blood formation, and for this reason their values are above the expected level. In such circumstances the fecal urobilinogen and Cr^{51} red cell survival should serve only as destruction indices.

Ineffective erythropoiesis was demonstrated in patients with refractory normoblastic anemia. The total erythropoiesis as determined by bone marrow plasma iron turnover and fecal urobilinogen production indices was about five times normal; however, the effective erythropoiesis, as shown by the reticulocytes, Fe^{59} utilization and Cr^{51} survival production indices, was poor, giving the bone marrow an efficiency of 15 and 31 per cent, respectively. In contrast, patients with aplastic anemia have a poor total erythropoiesis and, as a result of this, the effective erythropoiesis is poor too.

The similarity in the peripheral blood pictures (anemia, absolute or relative reticulocytopenia) between these two disorders was responsible for classifying them under one condition, namely, aplastic anemia. In reviewing reports on aplastic anemia in the literature [*33–36*] the point was made that a small percentage of patients with the peripheral blood findings of aplastic anemia paradoxically had a hyperplastic bone marrow. Luzzatto [*37*] referred to these patients as having "pseudoaplastic anemia." Later, this entity was called "refractory anemia" when its refractoriness to common antianemic agents and splenectomy was noted [*38,39*]. The demonstration of an increased number of sideroblasts in the bone marrow of these patients suggested an abnormality in iron metabolism [*40*]. Dacie et al. [*41*] established the presence of ineffective erythropoiesis in this disorder. To differentiate it from megaloblastic non-responsive anemia, the term refractory normoblastic anemia was given. Loeb et al. [*42*] demonstrated poor utilization of radioiron in patients with refractory anemia, and improvement with steroid therapy or splenectomy. The possible relationship of this disorder to preleukemic states, di Guglielmo disease, aplastic anemia, hypersplenism and refractory megaloblastic anemia has been considered by Vilter et al. [*43*] in a recent publication. The occurrence of this disorder as a temporary phase preceding other hematologic diseases, such as aplastic anemia and leukemia, has also been noted [*44–46*].

Group 4. Miscellaneous. The last group consisted of six patients. (Tables VII and VIII.) Two had hemochromatosis, with almost normal erythrokinetic studies except for the plasma iron turnover and the Fe^{59} utilization production indices. (Table VIII.) The slow rate of plasma radioiron clearance and poor utilization of radioiron may give an erroneous impression that total

erythropoiesis in hemochromatosis is poor. The increased concentration of iron in the labile and storage pools most probably is responsible for the dilution of radioiron and the results obtained [*47,48*]. This is further substantiated in Case II in which there was an improvement of red cell utilization of radioiron from 50 to 64 per cent after venesection of 6,000 ml. of blood over a period of four months.

The next three patients (Cases III, IV and V) had a megaloblastic anemia due to malabsorption of vitamin B_{12}, acute di Guglielmo disease and polycythemia vera, respectively. Total erythropoiesis was increased markedly in the patients with megaloblastic anemia and di Guglielmo disease as compared to the patient with polycythemia vera in whom total erythropoiesis was slightly more than normal. Because of the ineffective erythropoiesis in megaloblastic and di Guglielmo disease, the patients were anemic, whereas in polycythemia vera, in which the efficiency of the bone marrow is normal, the patient had erythrocytosis. In pernicious anemia [*49*] and tropical sprue [*50*] total erythropoiesis is increased approximately five times normal and seems to change very little in the early stage of vitamin B_{12} therapy. However, this vitamin does improve effective erythropoiesis and eventually both total and effective erythropoiesis approach normal. Serum iron levels, usually elevated in untreated patients, decrease rapidly upon treatment with vitamin B_{12}. In addition to ineffective erythropoiesis in the patient with di Guglielmo disease there is a striking discrepancy between the elevated reticulocyte count and the normal Cr^{51} red cell survival, in the absence of blood loss or specific therapy. In this situation, the reticulocyte count cannot be used as an index of effective red cell production, since it does not represent controlled production of red cells or controlled delivery of red cells from the bone marrow to the peripheral circulation. Baldini et al. [*51*] have studied the anemia of di Guglielmo syndrome in eleven patients in whom ineffective erythropoiesis was demonstrated. The term "heme-diversion" was used to describe the discrepancy between the increased excretion of fecal urobilinogen and the relatively slightly altered red cell survival determinations.

The last case (Case VI) included in this series of miscellaneous diseases is quite unusual. The patient, a fifty-seven year old white woman, presented herself with anemia and hepatosplenomegaly. The peripheral blood picture showed pancytopenia (normocytic and normochromic anemia, leukopenia and thrombocytopenia), increased reticulocyte count but no immature forms of the myeloid and erythroid series. Several bone marrow aspirations and one bone marrow biopsy specimen revealed hypoplasia and a moderate degree of myelofibrosis. Splenectomy was performed. The spleen was congested and showed no evidence of extramedullary hemopoiesis. On gross examination, the liver looked normal. The peripheral blood picture improved after splenectomy although repeated bone marrow aspirations revealed no change. Erythrokinetic studies were performed before and after splenectomy. Total erythropoiesis was increased two to three times normal without significant evidence of ineffective erythropoiesis. Although erythrokinetically there was evidence of increased red cell formation, this could not be supported by several bone marrow examinations. The most likely explanation is that red cells are being formed in this patient in bones inaccessible to the usual forms of examination.

SUMMARY AND CONCLUSIONS

Erythrokinetic studies were performed in thirty-seven subjects, including patients with thalassemia, abnormal hemoglobins, myelosclerosis and extramedullary hemopoiesis, chronic myelogenous leukemia, aplastic anemia, refractory normoblastic anemia and other miscellaneous disorders. The erythropoiesis production indices were calculated by applying the hematologic data obtained to appropriate formulas.

Ineffective erythropoiesis was observed in the following conditions: thalassemia major, extramedullary hemopoiesis, refractory normoblastic anemia, megaloblastic anemia and di Guglielmo disease. It was absent in the hemoglobinopathies, chronic myelogenous leukemia, aplastic anemia, hemochromatosis, hypersplenism and polycythemia vera.

The uptake of radioiron by spleen as measured *in vitro* (after removal of the organ) was not significant, even in extramedullary hemopoiesis. The presence of a large spleen did not seem to influence (1) red cell utilization of radioiron, (2) blood volume, (3) the fall in the blood of Cr^{51} radioactivity in the first twenty-four hours after injection of the radioactive material beyond the expected rate of red cell destruction, or directly, (4) the radioiron clearance rate.

The limitations inherent in the use of these diagnostic tools have made it advisable to rely

on as many indices as possible in the study of the mechanisms of anemia. Moreover, the intrinsic limitations of the indices in measuring erythropoiesis (whether total or effective) in all types of anemia must be clearly realized.

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Syndrome of Iron Deficiency Anemia, Hepatosplenomegaly, Hypogonadism, Dwarfism and Geophagia*

ANANDA S. PRASAD, M.D.,† JAMES A. HALSTED, M.D.‡ *and* MANUCHER NADIMI, M.D.
Shiraz, Iran

IN 1958 a twenty-one year old man entered the hospital presenting these clinical features: severe iron deficiency anemia, hepatosplenomegaly, short stature and marked hypogonadism. He gave a history of geophagia for several years and his diet was poor in animal protein. There was no evidence of blood loss or hook worm infestation, and the anemia promptly responded to oral iron therapy alone. Following this therapy the size of the liver and spleen decreased markedly and the genitalia began to develop. Results of all the liver function tests including serum protein levels were within normal limits, with the exception of the serum alkaline phosphatase level which was elevated. Roentgenograms of the bones revealed delayed skeletal maturation. The testis on biopsy was infantile. Clinically no evidence for hypothyroidism or hypoadrenalism could be elicited.

During the past two years, ten additional patients with a similar clinical picture have come to our attention. Eight of these patients have been studied in detail at the Nemazee Hospital where adequate facilities existed for usual clinical and laboratory examinations.§ Three were seen in a more superficial way at the Saadi Hospital, a government institution attached to the Shiraz Medical School. Figure 1 illustrates the general appearance of four of the patients.

The syndrome appears to be common in Iran. Although it has apparently been reported only once before, from Turkey [*1*], detailed descriptions of individual cases were not given. It therefore appears worthwhile to report the details of our eleven cases. The clinical and laboratory data of significance have been tabulated in Tables I and II.

§ We are indebted to Dr. M. Samimian whose interest in this problem prompted him to transfer five of the patients to the Nemazee Hospital for study by us.

CASE REPORTS

CASE 1. A twenty-one year old man (H. Z.), entered the hospital complaining of weakness of ten years' duration. At the age of eleven, when he began working in the rice fields, he noticed weakness, easy fatigability, dyspnea and palpitation. For four years he has been unable to work, has been pale, and believes he has had fever each night. Growth and sexual development have always been retarded.

During childhood and up to the present time the patient has been in the habit of eating clay. The dietary intake consisted merely of wheat bread with a little milk and potatoes daily. He rarely had any meat, eggs, chicken or vegetables, but was able to have some pomegranates and melon at times. There were two brothers and two sisters all living and well. One sister died at eighteen with edema and jaundice, and two others died in early childhood. A third brother, aged twenty-two, had severe anemia, hypogonadism, dwarfism, and also congenital abnormalities chiefly involving the extremities; he was mentally retarded. This brother, as well as the patient, was a clay eater. None of the other siblings had this habit.

Physical examination revealed a pale undernourished man of twenty-one who appeared about ten years of age. His height was 135 cm., weight 29.5 kg. The temperature was 37.4°C. and respirations 20 per minute. The heart was enlarged to the left, rate 100, regular. The blood pressure was 105/55 mm. Hg. A loud systolic murmur was heard at the apex. There

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† Present address: Metropolitan Hospital and Clinics, Detroit, Michigan.
‡ Present address: NAMRU 3, American Embassy, Cairo, United Arab Republic.

FIG. 1. From left to right: Case V, age 21, height 4 feet, 11½ inches; Case VI, age 18, height 4 feet, 9 inches; Case III, age 18, height 4 feet, 6 inches; Case I, age 21, height 4 feet, 7 inches. Staff physician at left is 6 feet in height.

was some engorgement of the neck veins and slight pitting edema of the ankles. The lungs were clear. Skin and hair were normal. The nails showed koilonychia.* There was some distention of the abdomen, with minimal ascites. The liver and spleen were both palpable 4 cm. below the costal margin. The external genitalia were infantile and no prostatic tissue was palpable. There was no pubic, axillary or facial hair.

The hemoglobin was 3.5 gm. per cent, hematocrit 17 per cent, white blood count 8,900 with normal differential. The mean corpuscular hemoglobin concentration was 23 per cent. Several urine and stool examinations were within normal limits.

The serum iron was 62 μg. per cent, the total iron binding capacity was 495 μg. per cent. Two iron absorption tests were unsuccessful because the patient vomited the test dose of ferrous gluconate each time.

The serum bilirubin, direct, was 0.04, total 0.1 mg. per cent. Result of the thymol turbidity test was 3.7 units, the cephalin flocculation test 2 plus at forty-eight hours, alkaline phosphatase was 7.6 Bodansky units on admission and about the same subsequently. Serum glutamic oxaloacetic transaminase (subsequently expressed as SGOT) was 23 units per ml., serum glutamic pyruvic transaminase (subsequently expressed as SGPT) 7 units per ml. The prothrombin content was 100 per cent.

Blood urea nitrogen, serum cholesterol, calcium, inorganic phosphorus and uric acid levels were all normal. Results of a serologic test for syphilis and the Kahn test were negative. The result of a water test (Soffer) for adrenal function was within normal limits.

The serum total protein was 6.2 gm. per cent. Paper electrophoresis revealed the albumin to be 46.7 per

FIG. 2. Characteristic spoon nails (koilonychia), present in a majority of the patients.

* Figure 2 shows the characteristic spoon nails (koilonychia) noted in seven of the patients, and pathognomonic of iron deficiency anemia.

TABLE I

SALIENT CLINICAL FEATURES

Case No.	Age (yr.)	Height (cm.)	Weight (kg.)	Appearance	Liver (cm. below costal margin)	Spleen (cm. below costal margin)	Genitalia and Secondary Sexual Characteristics	Miscellaneous Data
I	21	135	29.5	That of a 10 year old boy; pallor; dyspnea	4	4	No public, axillary or facial hair; infantile external genitalia; no prostate felt	Geophagia of nearly 10 to 12 years duration; congestive failure on admission; after treatment with oral iron, hepatosplenomegaly decreased; edema, ascites and engorged neck veins disappeared; gained 16 lb.; after 8 months sexual growth and function developed
II	15	133	27.7	That of an 8 year old boy; pallor; and chronically ill	4	7	No pubic, axillary or facial hair; infantile external genitalia; prostate small	Geophagia for 12 to 13 years, gained 6 lb.; six weeks after oral iron treatment, spleen was 2 cm. below the costal margin and liver size had decreased
III	18	133	30.4	That of a 10 year old boy; pallor and chronically ill	3	3	No pubic, axillary or facial hair; small external genitalia (similar to 10 year old)	Geophagia for several years; gained 8 lb.; twelve weeks after treatment liver and spleen were not palpable; after nine months sexual growth and function developed; spoon nails disappeared
IV	21	141	30.4	That of a 14 year old boy; pallor; dyspnea	8	4	No pubic, axillary or facial hair; infantile external genitalia, prostate very small	Geophagia of several years' duration; gained 15 lb.; liver and spleen size decreased after treatment with oral iron
V	21	150	42.3	That of a 15 year old boy. Pallor and dyspnea	7	3	No pubic axillary or facial hair. Small external genitalia	Geophagia for many years; fourteen weeks after treatment with iron, liver 3 cm. below the costal margin and spleen not palpable; gained 14 lb. after 8 months sexual growth and function had developed
VI	18	143	37.5	That of a 14 year old boy	5	3	No pubic, axillary or facial hair; small genitalia	Geophagia of several years; after 16 weeks of treatment, liver and spleen normal in size, testes became larger and pubic hair appeared; gained 24 lb.
VII	14	132	33.6 (during congestive failure), 27.6 (after he lost edema)	That of a 9 year old boy	6	2.5	No pubic, axillary or facial hair; small testes	Geophagia of several years; six weeks after oral iron therapy, spleen tip just palpable; this patient was in congestive failure due to anemia on admission; gained 13 lb. in 6 weeks
VIII	14	118	19.1	That of an 8 year old boy	2	1	No axillary facial or pubic hair; infantile genitalia	Geophagia; ate charcoal all his life; nine weeks after admission liver and spleen were barely palpable
IX	18	—	33.6	That of a 12 year old boy	Enlarged	Enlarged	No pubic, axillary or facial hair; small external genitalia	Geophagia of several years' duration; enlarged parotid glands; follow-up not available
X	21	—	37.7	That of a 12 year old boy	Not palpable	Palpable at costal margin	No pubic, axillary or facial hair; small external genitalia	Follow-up not available
XI	21	145	35.5	Much younger than stated age	Enlarged	Enlarged	No pubic, axillary or facial hair; genitalia very small	Geophagia; follow-up not available

cent, alpha-globulin was 4.8 per cent, alpha$_2$-globulin 12.3 per cent, beta-globulin 15.5 per cent and gamma globulin 20.7 per cent. Result of a xylose absorption test was within normal limits. Gastric analysis performed before and six weeks after treatment revealed no free hydrochloric acid after histamine stimulation on either occasion. Fecal urobilinogen was normal.

A bone marrow biopsy specimen revealed erythrocytic hyperplasia. A liver biopsy specimen revealed normal liver tissue. The testicular biopsy specimen showed prepuberal testis.

The roentgenogram of the chest showed the heart to be moderately enlarged to right and left. Barium enema, upper gastrointestinal series, intravenous pyelogram and gallbladder series were all within normal limits. A skeletal survey showed good mineralization of bone; roentgenograms of the skull revealed no abnormalities. Roentgenograms of the long bones indicated the bone age to be less than fourteen years.

Two weeks after admission oral iron therapy with Ferrosan, one tablet three times a day, was started. The reticulocytes rose to 8 per cent ten days later. Eight weeks after treatment was started the hemoglobin had risen to 13.7 gm. per cent, the hematocrit to 47 per cent, and the red blood cell count was 5.8 million per cu. mm. Mean corpuscular hemoglobin concentration was 29 per cent. The liver and spleen had both receded in size.

Although mild cardiac failure was present on admission, this cleared up with bed rest and therapy for anemia, without digitalis therapy. The patient gained 16 pounds after ten weeks of hospitalization and upon discharge was normal in strength, mental activity

TABLE II
SIGNIFICANT LABORATORY DATA
(BEFORE TREATMENT)

Case No.	Hemoglobin (gm. %)	Hematocrit (vol. %)	Serum Iron (μg. %)	Total Iron-Binding Capacity (μg. %)	Oral Iron Absorption Test (μg. %)		Serum Alkaline Phosphatase* (Bodansky units)	Roentgenograms	Liver Biopsy Specimen	Follow-up Data
					Before	After				
I	3.5	17	62	495	...	...	7.6	Bone age less than 14 years	Normal	Eight weeks after treatment with oral iron, hemoglobin was 13.7 gm. % and hematocrit was 47 vol. %; after 8 months hematocrit was 49 vol. %
II	4.2	18	44	570	44	86	7.6	Approximate bone age 10 years; skull roentgenogram showed changes similar to those seen in thalassemia	1-plus fat	Ten weeks after oral iron therapy hemoglobin was 12.6 gm. % and hematocrit was 42 vol. %
III	6.0	23	82	573	82	176	5.0	Approximate bone age 10 years	Fatty with moderate fibrosis and cellular infiltration	Twelve weeks after oral iron therapy hemoglobin was 16.1 gm. % and hematocrit was 52 vol. %
IV	7.7	30	68	541	68	186	15.2	Bone age less than 14 years	Fatty liver	After 6 weeks of oral iron therapy hemoglobin was 12.3 gm. % and hematocrit was 42 vol. %
V	4.2	20	73	419	73	168	9.8	Bone age approximately 15 years	Normal	After 6 weeks of oral iron therapy hemoglobin was 13.4 gm. %, hematocrit 45 vol. %; after 8 mo. hemoglobin was 15 gm. %, hematocrit 46 vol. %
VI	5.3	21	51	536	51	164	8.3	Bone age approximately 13 years	Normal	After 8 weeks of oral iron therapy, hemoglobin was 14.7 gm. %, hematocrit 47 vol. %
VII	3.0	11	24	502	24	406	5.2	Bone age approximately 11 years	Cirrhosis repeat biopsy 13 weeks later reported as "fibrosis"	Six weeks after oral iron therapy hemoglobin was 13.0 gm. %, hematocrit 40 vol. %
VIII	2.8	14	30	365	30	358	6.4	Bone age about 6 years	Not performed	Eight weeks after admission hemoglobin was 11.2 gm. %, hematocrit 41 vol. %
IX	3.2	15	78	...	...	...	10	Bone age approximately 12 years	Slight fatty infiltration	After 20 weeks of oral iron therapy, hemoglobin was 12.4 gm. %
X	3.0	...	16	480	...	...	7.0	...	Normal	Follow-up data not available
XI	3.9	23	25	...	...	...	...	...	Normal	Hemoglobin rose to 12.1 gm. % after 6 weeks and hematocrit to 46%; serum iron rose to 137

* Subsequent values noted in case protocols. Figure 3 lists changes occurring in three cases followed up over a prolonged period.

and behavior. No change in sexual characteristics was observed at this time. His temperature averaged 37.5°C. during the first six weeks but was normal after that time.

A follow-up visit eight months after discharge revealed the following: he had been eating quite an adequate diet consisting of meat, bread, rice and fruit daily. He now had erections and questionable ejaculation. Examination revealed the liver to be barely palpable and the spleen 1.5 cm. below the costal margin. There was no ascites. Pubic hair was present but there was no beard. The hematocrit was 49 per cent, the serum alkaline phosphatase 15 Bodansky units.

CASE II. A fifteen year old boy (G. S.), was admitted with the chief complaints of pallor, weakness and palpitation of twelve years' duration. He started eating clay (geophagia) at the age of three, gradually lost his appetite and became pale and weak. His

parents, two brothers and two sisters are living, normally developed and well. No one else in the family practiced geophagia. The patient's diet consisted mainly of wheat bread, approximately 200 gm. per day. Occasionally he ate mast (yogurt). He never had any milk, eggs or butter. Once in eight to ten days he would eat meat (roughly 400 gm. of meat for seven persons in the family). The diet was also poor in vegetables.

The patient weighed 27.7 kg. and the height was 133 cm. Temperature was 37.5°C., pulse 100 per minute, blood pressure 100 mm. Hg systolic, 40 mm. Hg diastolic. His appearance was that of an eight year old child. He looked underdeveloped, poorly nourished, pale and chronically ill. Spoon nails were present. A systolic murmur was heard in the precordial region. The liver edge was palpable 4 cm. below the right costal margin and the spleen was enlarged 7 cm. below the left costal margin. No ascites or edema was present. The external genitalia were that of a three year old child. Testes and prostate were present but small. Pubic, axillary and facial hair was not present. The skin and hair were normal.

The hemoglobin was 4.2 gm. per cent, hematocrit 18 per cent, total leukocyte count 4,000 per cu. mm. with normal differential, red blood cell count 2.6 million per cu. mm., platelets 130,000 per cu. mm. Mean corpuscular volume was 69, mean corpuscular hemoglobin 16 per cent, and mean corpuscular hemoglobin concentration 24 per cent. Several routine examinations of urine and stool were within normal limits.

The serum iron was 44 μg. per cent, total iron binding capacity was 570. Four hours after an oral dose of 240 mg. of ferrous gluconate the serum iron increased to 86 μg. per cent. The serum bilirubin was, direct 0.07 and total 0.3 mg. per cent. Bromsulfalein retention was 3.3 per cent in forty-five minutes, results of the thymol turbidity test was 3.7 units, the cephalin flocculation test 2 plus in twenty-four and forty-eight hours. The serum alkaline phosphatase level three days after the patient had been in the hospital was 7.6 Bodansky units, subsequently it was 8.6 and 8.8 units. SGOT was 8 units per ml., SGPT 8 units per ml.

Blood urea nitrogen, carbon dioxide, serum chloride, calcium and inorganic phosphorus levels were all normal. Results of the serologic test for syphilis and the Kahn test were negative. Serum total protein was 6.1 gm. per cent of which albumin was 64 per cent, alpha globulin 10.7 per cent, beta globulin 11.5 per cent and gamma globulin 13.8 per cent. Result of a xylose absorption test was normal. Gastric juice revealed no free acid after histamine stimulation. Fecal urobilinogen excretion was normal.

A roentgenogram of the chest revealed the heart to be enlarged in the transverse diameter. The roentgenogram of the skull revealed widening of the vault, with trabecular striations perpendicular to the vault and patchy areas of osteoporosis in the parietal bones. Roentgenograms of the long bones indicated the approximate bone age to be eight to ten years. Upper and lower gastrointestinal series, roentgenograms of the gallbladder and intravenous pyelogram revealed no abnormalities. A bone marrow biopsy specimen was normal. A needle biopsy specimen of the liver revealed 1-plus fatty infiltration. The testicular biopsy specimen revealed prepuberal testis.

Two weeks after admission, oral iron therapy with Ferrosan, one tablet three times a day, was started. Reticulocytosis up to 6 per cent was observed. Ten weeks following this treatment the hemoglobin was 12.6 gm. per cent, hematocrit measured 42 per cent and mean corpuscular hemoglobin concentration was 30 per cent. Six weeks after treatment the spleen was palpable 2 cm. below the left costal margin and the liver edge was felt 3 cm. below the right costal margin. The patient gained 6 pounds of body weight during hospitalization. The caloric intake in the hospital varied from 2,100 to 2,300 calories and he received 120 gm. of protein per day. He was discharged after ten weeks of hospitalization and was advised to continue iron treatment.

During the first six weeks of hospitalization his temperature ranged between 37° and 38°C. but he became afebrile on iron treatment alone.

CASE III. This eighteen year old boy (J. R.), was admitted to the hospital with the chief complaint of weakness since childhood. His other complaints included exertional dyspnea and palpitation. He gave a history of geophagia for several years. His diet had been very poor, being essentially wheat bread, with grapes during the summer. Milk, meat or eggs were available to him only occasionally. His four sisters and two brothers are living and well. One of his cousins (Case VI) has a similar disease.

On admission the temperature was 38°C. Pulse rate was 80 per minute, blood pressure 108 systolic mm. Hg, 68 diastolic mm. Hg. The height was 133 cm. and weight 30.4 kg. The patient had the general appearance of a ten year old boy. He was underdeveloped, undernourished, pale and chronically ill. Skin and hair were normal. Axillary, pubic and facial hair was absent. Koilonychia was present. The liver was enlarged, the edge being felt 3 cm. below the right costal margin. The spleen was felt 3 cm. below the left costal margin. A systolic murmur was heard at the apex. The external genitalia and prostate were small and resembled that of a ten year old boy.

The hemoglobin on admission was 6 gm. per cent, the hematocrit 23 per cent. The total leukocyte count, differential count and platelet count were within normal limits. Prothrombin time, bleeding and clotting time were also normal. Several routine examinations of urine and stool revealed no abnormalities.

The serum bilirubin, direct, was 0.2 mg. per cent and total 1.3 mg. per cent. The result of the thymol turbidity test was 3.1 units, cephalin flocculation test

1 plus in twenty-four and forty-eight hours; bromsulfalein retention was 1 per cent in forty-five minutes. The serum alkaline phosphatase soon after admission was 5 Bodansky units but a few weeks later it increased to 8.3 and 13.2 units (numerous subsequent determinations are noted in Figure 3). The serum total protein was 6.6 gm. per cent, of which albumin was 48.5 per cent, alpha globulin 17 per cent. SGOT was 18 units per ml., SGPT was 17 units per ml.

The serum iron was 82 μg. per cent, total iron binding capacity was 573 μg. per cent. Four hours after a single oral dose of 240 mg. ferrous gluconate the serum iron increased to 176 μg. per cent. Result of a glucose tolerance test was normal. The serum sodium, potassium, calcium, inorganic phosphorus, blood urea nitrogen and water test (Soffer) for adrenal function were all within normal limits. The basal metabolic rate was plus 15 per cent. Fecal urobilinogen was normal. Gastric juice analysis failed to reveal the presence of free acid after histamine injection. An electrocardiogram was normal. A roentgenogram of the chest was non-contributory. Upper and lower gastrointestinal series, roentgenograms of the gallbladder, and an intravenous pyelogram were all within normal limits. Roentgenograms of the long bones revealed the bone age to be ten years. Roentgenograms of the skull were within normal limits. A bone marrow biopsy specimen was normal.

Eleven weeks after admission, surgical liver biopsy was performed. Grossly, the liver appeared normal. Histologically, it showed fatty infiltration, moderate fibrosis and cellular infiltration. The spleen appeared normal in size. The portal pressure was 30 mm. of H_2O. Histologically the testis revealed immature seminiferous tubules with germinal cells in the earliest stage of maturation, and the over-all picture was that of prepuberal testis. A gastric biopsy specimen was obtained by means of a Crosby tube and this was non-contributory except for the presence of a few inflammatory cells.

Four weeks after admission oral iron therapy with Ferrosan, one tablet three times a day, was started. Twelve weeks later the hemoglobin was 16.1 gm. per cent and the hematocrit 52 per cent. The size of the liver and spleen decreased considerably and were normal in size at the time of discharge (sixteen weeks after admission). The temperature ranged between 37° to 38°C. before treatment but one week after starting therapy it became normal. During the period of hospitalization, the patient gained 8 pounds.

He was seen in follow-up nine months after discharge. At this time he had gained 3 more pounds. The koilonychia had disappeared. The liver and spleen were not palpable and the abdomen was of normal contour. There was a marked growth of pubic hair. The testes and penis were considerably increased in size. He now had erections and ejaculations. Hemoglobin was 14.8 mg. per cent, hematocrit 47 per cent, and alkaline phosphatase 12.5 Bodansky units.

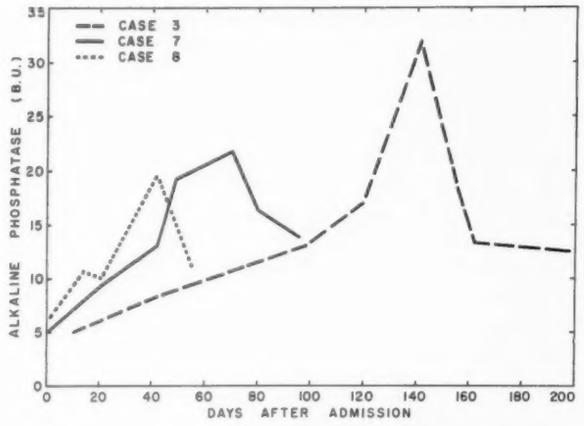

FIG. 3. Graph showing serum alkaline phosphatase changes associated with hospitalization and a well balanced diet. These curves are from determinations made in Case III, VI and VIII.

CASE IV. A twenty-one year old man (M. M.), was admitted with the complaints of weakness and pallor since childhood. Four years previously he had had to stop working as a shepherd. He has had epigastric distress at times for the past five years. Four years previously he had malaria. The patient has been addicted to the eating of dirt since childhood. He has one brother who takes the same diet as the patient but is not afflicted with geophagia and is entirely healthy. The parents died of unknown cause and there are no other siblings. The patient's diet in general was restricted to wheat bread, rice and sugar regularly, with melon, fruit, sour milk and a little meat only at certain seasons during the year.

The past history and system review were otherwise non-contributory. Physical examination showed a man of twenty-one who appeared to be about fourteen, but with a wrinkled skin. There was no facial, pubic or axillary hair. The temperature was 37.8°C., pulse 104, blood pressure 120/80 mm. Hg. Weight was 30.4 kg., height 141 cm. There was moderate cardiac enlargement and a grade 2 systolic murmur at the apex. The lungs were clear and there was no edema. The liver was palpable 8 cm. below the costal margin and the spleen was felt 3 to 4 cm. below the costal margin. The testes were of a size expected in a very young boy. The prostate was small.

On admission the hemoglobin was 9 gm. per cent; it was 7.7 gm. per cent nine days later. The hematocrit was 30 per cent. Red blood count was 4.8 million per cu. mm. Mean corpuscular volume was 62 cu. μ, mean corpuscular hemoglobin 18 μμgm., and mean corpuscular hemoglobin concentration 30 per cent. The white blood cell count was 7,500 per cu. mm. with normal differential. Serum iron was 68 μg. per cent, and rose to 186 μg. per cent four hours after an oral dose of

240 mg. of ferrous gluconate. The total iron binding capacity was 541 μg. per cent.

The serum bilirubin was 0.04 mg. per cent direct and 0.08 total. Serum alkaline phosphatase was 15.2 Bodansky units on admission with subsequent values of 12.8, 12.7, 10.3 and 10.8 units during the hospital stay. Result of the thymol turbidity test was 5 units, the cephalin flocculation test 2 plus after forty-eight hours, SGOT 46 units and SGPT 43 units. The prothrombin content was 100 per cent. Serum total protein was 8 gm. per cent of which albumin made up 49.5 per cent, alpha$_1$-globulin 4.1 per cent, alpha$_2$-globulin 10.9 per cent, beta globulin 14.3 per cent and gamma globulin 21.2 per cent.

Serum calcium, inorganic phosphorus, cholesterol and uric acid levels, and fecal urobilinogen were all within normal limits. The result of a xylose absorption test was normal. Free acid was present in the gastric juice after histamine stimulation. Several urinalyses and stool examinations for occult blood and parasites revealed no abnormalities. Results of a serologic test for syphilis and Kahn tests were negative. The reaction to a water test for adrenal function was normal.

Three weeks after admission a surgical biopsy specimen of the liver showed moderate fatty metamorphosis. The gross appearance was a mottled yellowish brown color, firm but smooth, and about 50 per cent larger than normal. Four weeks later a needle biopsy specimen also showed moderate fatty changes.

A testicular biopsy specimen showed seminiferous tubules identical to those seen in infancy and very early childhood. A bone marrow biopsy specimen was normal. Roentgenograms of the chest showed moderate cardiac enlargement and clear lung fields except for a few calcified nodules. Cholecystogram, upper gastrointestinal series, barium enema and intravenous pyelogram were all within normal limits, except for a left bifid renal pelvis and ureter. A skeletal survey revealed normal mineralization with a bone age of less than fourteen years. A roentgenogram of the skull showed a normal sella turcica and underdeveloped maxillary sinuses.

The patient was treated with ferrous sulfate, 0.2 gm. three times a day, after the studies were completed. His hemoglobin rose from 7.7 gm. per cent to 12.3 gm. per cent after six weeks. The hematocrit rose to 42 volume per cent. A slight reticulocytosis of 2 per cent was observed a few days after iron therapy was started. The patient's weight increased from 30.4 to 37.2 kg. He had a low grade fever with temperatures up to 37.5°C. until he had been treated with iron for three weeks, after which he was afebrile.

He was discharged after ten weeks of hospitalization. A visit was made to his village two months later. He was in excellent health and was working full time as a shepherd.

CASE V. A twenty-one year old man (G. A.), entered the hospital on November 11, 1959, complaining of dyspnea on exertion and weakness since the age of thirteen. Growth was very slow and the secondary sex characteristics and facial and axillary hair had not developed normally. He had night blindness for several years. He had eaten clay all his life. The diet consisted of bread, occasional milk, meat twice a month, fruits and vegetables at irregular intervals. Several years before he had had an abscess of the anterior part of the neck which drained for a long time. Six months before he had burned the lower part of his left leg and an indolent ulceration persisted. His parents were dead; three siblings are alive and well.

Physical examination revealed a very pale man who appeared about fifteen years old. Weight was 42.3 kg., height 150 cm., blood pressure 130/85 mm. Hg, pulse 124. The face was puffy and both parotid glands were enlarged. There was no facial, axillary or pubic hair. The testes, penis and prostate were small. The nails were spoon-shaped. The heart was moderately enlarged to the right and left with a grade 2 systolic murmur at the apex. The lungs were clear. The abdomen was distended but no ascites could be demonstrated. The liver was felt 7 cm. and the spleen 3 cm. below the costal margin.

The hemoglobin was 4.2 gm. per cent, hematocrit 20 per cent, red blood cell count 3.2 million per cu. mm., white blood cell count 8,200 per cu. mm. with differential count showing 45 per cent polymorphonuclears, 40 per cent lymphocytes, 2 per cent monocytes, and 13 per cent eosinophils. Mean corpuscular volume was 62 cu. μ, mean corpuscular hemoglobin 13 μμgm., and mean corpuscular hemoglobin concentration 21 per cent.

The serum iron was 73 μg. per cent and four hours after an oral dose of 240 mg. of ferrous gluconate it rose to 168. The total iron-binding capacity was 419 μg. per cent.

Several urinalyses were negative. Two stool specimens were negative for occult blood and parasites.

The serum bilirubin was 0.08 mg. per cent direct and 0.3 total. Bromsulphalein retention was 4 per cent at forty-five minutes, serum alkaline phosphatase was 9.8 Bodansky units on admission with values of 8.5, 7.3 and 6.4 on subsequent examination over a four-month period. The result of the thymol turbidity test was 3.1 units, the cephalin flocculation test 1 plus. SGOT was 20 units and SGPT 26 units. Serum electrophoresis revealed a total protein of 8 gm. per cent, of which albumin was 40.7 per cent, alpha$_1$-globulin 3.5 per cent, alpha$_2$-globulin 8.2 per cent, beta globulin 12.2 per cent and gamma globulin 35.4 per cent. Serum calcium, phosphorus, uric acid, cholesterol and blood urea nitrogen levels and fecal urobilinogen were all within normal limits. The reaction to a xylose absorption test was normal. Gastric analysis showed no free hydrochloric acid after histamine stimulation. The result of a water test for adrenal function was normal.

A bone marrow biopsy specimen was normal.

Needle biopsies of the liver performed three weeks and two months after admission revealed no abnormalities. A testicular biopsy specimen showed seminiferous tubules identical to those seen in infancy and early childhood. A jejunal biopsy specimen obtained with a Crosby tube showed normal histology.

The heart was enlarged to the right and left, with normal lung fields. Barium enema, upper gastrointestinal series, oral cholecystogram, intravenous pyelogram and roentgenograms of the skull were all within normal limits. The bones of the extremities showed delayed epiphyseal closure, with a bone age of fifteen years.

After studies were completed, treatment with ferrous sulfate was begun (one month after admission). The hemoglobin level had risen from 4.2 to 6 gm. per cent and the hematocrit from 20 to 29 per cent, before iron therapy, presumably due to the hospital diet. After six weeks of iron therapy the hemoglobin rose to 13.4 gm. per cent and hematocrit to 45 per cent. A reticulocytosis of 3 per cent was observed. The patient's weight increased from 42.3 to 48.7 kg. The indolent ulcer on the leg required operations consisting of excision, vein ligation and grafting. The patient was discharged after four and a half months. At this time the liver had decreased markedly in size and the spleen was no longer palpable.

The patient was seen in follow-up eight months after discharge. He had been taking a fairly good diet. He now had penile erections and questionable ejaculation. Pubic hair had appeared. The liver and spleen were barely palpable. The hemoglobin was 15 gm. per cent, hematocrit 46 per cent, and serum alkaline phosphatase 9.3 Bodansky units.

CASE VI. An eighteen year old boy (S. R.) entered the hospital on November 21, 1959, complaining of weakness and pallor since childhood. During the past few years he had experienced dyspnea and palpitation on exertion and his abdomen had been protuberant. He had dizziness and headache, also constipation and indigestion at times. Recently he noticed that he could not see in the dark.

For most of his life, starting at the age of two, he had the habit of eating clay (geophagia). His diet consisted chiefly of wheat bread. However, he had meat daily and eggs twice a week during the spring months only. He ate grapes when available, but almost no vegetables. He had a glass of milk every five or six days.

The past history was otherwise non-contributory. Father and mother were living and well. One brother, aged four, was very pale and weak. Six sisters were entirely healthy. A cousin (Case III) has a similar disease.

Physical examination revealed a very pale man who appeared about fourteen, and had spoon-shaped nails. The temperature was 37.3°C., pulse 80, blood pressure 100/60 mm. Hg. The weight was 37.5 kg. and height 143 cm. The heart was of normal size and rhythm, but a grade 2 systolic murmur was heard at the apex. The lungs were clear. The abdomen was protuberant and the liver was palpable 5 cm. below the costal margin. The spleen was felt 3 cm. below the costal margin. There was no ascites or edema. There was no facial or axillary hair and a minimal amount of pubic hair. The external genitalia were small.

The hemoglobin was 5.3 gm. per cent, hematocrit 21 per cent, red blood cells 2.8 million per cu. mm., white blood cells 4,500 per cu. mm. with normal differential count. Mean corpuscular volume was 88 cu. μ, mean corpuscular hemoglobin 21 $\mu\mu$gm., and mean corpuscular hemoglobin concentration 18 per cent. Serum iron was 51 μg. per cent; four hours after an oral dose of 240 mg. of ferrous gluconate it rose to 164 μg. per cent. The total iron-binding capacity was 536 μg. per cent. Bleeding and clotting times were normal. Several urinalyses and stool examinations revealed no abnormalities.

Serum sodium, potassium, calcium, inorganic phosphorus, uric acid and blood urea nitrogen levels were within normal limits, as was the result of a glucose tolerance test, and fecal urobilinogen. The serum cholesterol was 105 mg. per cent.

A gastric analysis showed absence of free acid after histamine stimulation. Results of a xylose absorption test and the serologic test for syphilis were negative. An electrocardiogram was within normal limits.

Bromsulphalein retention was 3 per cent after forty-five minutes; the thymol turbidity test result was 5 units; serum alkaline phosphatase on admission was 8.3 Bodansky units and subsequent determinations were 6.8 and 8 Bodansky units. The serum total protein was 7.5 gm. per cent of which albumin was 56.5 per cent, alpha$_1$-globulin 3, alpha$_2$-globulin 7, beta globulin 15.5, and gamma globulin 18 per cent, respectively. The prothrombin content was 100 per cent.

Roentgenograms of the chest showed a normal-sized heart and clear lung fields. Upper gastrointestinal series, barium enema, gallbladder series, intravenous pyelogram were all within normal limits. A roentgenogram of the skull showed small osteolytic lesions varying from 1 to 5 mm. in diameter, chiefly in the parietal bones; one such lesion was present in the right ninth rib. Extremities showed normal mineralization with retarded maturation and a bone age of thirteen years. The osteolytic lesions were thought to be related to long-standing anemia.

A needle liver biopsy specimen showed normal liver tissue. A bone marrow aspiration was normal. A testicular biopsy specimen showed a prepuberal testis with immature seminiferous tubules and germinal cells in the earliest stage of maturation. In order to obtain further precise information relative to the state of the liver, a surgical biopsy of the liver was performed two months after admission. The liver was enlarged, extending 5 cm. below the costal margin but was

grossly of normal texture and color. The spleen was not palpated. The portal pressure was 200 mm. H_2O. Three biopsy specimens were taken from the edge and histologically were reported as normal.

The patient was treated with ferrous sulfate, 0.2 gm. three times a day, and a high protein, high calorie diet. His hemoglobin rose from its initial level of 5.3 gm. per cent to 14.7 gm. per cent after eight weeks. A reticulocytosis of 3 per cent was observed. Three and a half months after discharge a streptococcal throat infection developed and two weeks later acute glomerular nephritis with hypertension, hematuria and edema, from which he recovered after two months. His testes doubled in size, and pubic hair appeared. The liver and spleen became normal in size after five months' observation. His weight increased from 35.5 kg. on admission to 46.3 kg. on discharge. Shortly before discharge the gastric analysis was repeated and achlorhydria was still present.

CASE VII. A fourteen year old boy (H. Z.), was admitted with the chief complaints of abdominal protuberance, exertional dyspnea, palpitation, orthopnoea, edema of the feet and puffiness of the face, of one year's duration. His diet consisted of about 700 gm. of wheat bread per day and sour milk. Eggs and butter were available to him only once or twice a month. He ate meat twice or thrice in a year. He gave a history of eating clay for several years since childhood.

The patient appeared pale and acutely ill. His general appearance was that of a nine year old boy. His height was 132 cm. and weight 33.6 kg. The vital signs were as follows: blood pressure 120/80 mm. Hg, temperature 38.3°C., pulse 112 per minute and respirations 40 per minute. The neck veins were prominent, with visible pulsations in the sitting position. The face looked puffy. No facial, axillary or pubic hair was present. The apex beat was felt at the fifth intercostal space in the mid-clavicular line. A systolic murmur was present in the pulmonary area. Mild ascites was present. The liver edge was felt 6 cm. below the left costal margin. Both testes and external genitalia were small. Pitting edema of the lower extremities was noted.

The hemoglobin was 3 gm. per cent, hematocrit 11 per cent, total leukocyte count 7,300 per cu. mm. with normal differential count. Mean corpuscular hemoglobin concentration was 27 per cent. Bleeding, clotting and prothrombin times were normal. The result of a serologic test for syphilis was negative. Several stool and urine samples were examined but revealed no abnormalities. The venous pressure was 18.5 cm. of physiologic saline solution.

Serum bilirubin was normal. The result of the thymol turbidity test was 4.3 units, and zinc sulfate turbidity test 10.9 units. Bromsulfalein retention was 13 per cent in forty-five minutes (nine weeks later it was 1 per cent). The serum alkaline phosphatase soon after admission was 5.2 Bodansky units but three weeks later it was 9.4 and seven weeks after admission it was 19.2 Bodansky units. (Subsequent determinations are noted in Figure 3.) The serum total protein was 6.3 gm. per cent of which albumin was 28.7 per cent, alpha globulin 11.5 per cent, beta globulin 12.1 per cent, and gamma globulin 47.8 per cent. SGOT was 32 units per ml. and SGPT 17 units per ml. Total cholesterol was 245 mg. per cent, blood urea nitrogen 7 mg. per cent, fasting blood sugar 68 mg. per cent.

The serum iron was 24 μg. per cent and total iron-binding capacity 502 μg. per cent. Four hours after an oral dose of ferrous sulfate the serum iron rose to 406 μg. per cent.

The basal metabolic rate was plus 16 per cent. Result of a Soffer water test showed 1,000 ml. excreted in four hours after drinking 1,500 ml. Gastric analysis indicated free hydrochloric acid.

Esophagogram, upper gastrointestinal series and roentgenograms of the small bowel were all within normal limits. Roentgenograms of the long bones revealed the bone age to be that of an eleven year old child. Roentgenograms of the chest revealed the heart size to be enlarged and congestive changes in the lungs consistent with the diagnosis of congestive heart failure. Three weeks later the roentgenogram of the chest was within normal limits. Electrocardiogram revealed non-specific ST-T changes in precordial leads I to IV.

A needle biopsy specimen of the liver was compatible with the diagnosis of cirrhosis of the liver.

Since this patient had congestive heart failure, he was treated initially with a low salt diet, one injection of 2 cc. of mersalyl, and digitoxin. The low salt diet and digitoxin were discontinued after four weeks. Following this the patient became free of edema, the heart size returned to normal (on roentgenograms) and ascites disappeared. Bromsulfalein retention returned to normal. He was given Ferrosan, one tablet three times a day, starting one week after admission. Six weeks later the hemoglobin was 13 gm. per cent, the hematocrit was 40 per cent, and there was no evidence of congestive heart failure.

Thirteen weeks after admission the liver was 4 cm. below the right costal margin and the spleen tip was just palpable. At this time the serum total protein was 7.7 gm. per cent, with albumin 3.8 and globulin 3.9. A repeat liver biopsy specimen was interpreted as showing fibrosis of the liver.

The patient became afebrile after four weeks of iron therapy. His initial weight was 33.6 kg., but he lost 6 kg. after ten days; this weight loss was associated with treatment for congestive heart failure. Seven weeks later he again weighed 33.6 kg., a gain in tissue weight.

CASE VIII. A fourteen year old boy (S. J.), was admitted to the hospital with the chief complaints of paleness, weakness and palpitation of several years' duration. He gave a history of geophagia and eating charcoal for at least ten to twelve years. His diet con-

sisted mainly of wheat bread, approximately 600 gm. a day. Only during the spring was he able to obtain some meat. He ate fruits such as grapes, apples and pomegranates in the summer and fall.

The patient appeared about eight years old. The weight was 19.1 kg. and height 118 cm. Blood pressure was 100/56 mm. Hg, pulse 140 per minute, and respirations were normal. The patient appeared to be chronically ill and very pale. Koilonychia was present. A systolic murmur was heard in the precordial region. The liver edge was palpable 2 cm. below the right costal margin, the spleen was palpated 1 cm. below the left costal margin. No axillary, pubic or facial hair was present. The external genitalia and testes were atrophic and small, resembling that of a small child.

On admission the hemoglobin was 2.8 gm. per cent, the hematocrit was 14 per cent. Total leukocyte count was 5,100 per cu. mm. Mean corpuscular hemoglobin concentration was 20 per cent. The reticulocyte count was 0.3 per cent. The bleeding and clotting times were normal. Routine urinalysis was negative. Stool examination revealed ascariasis but no occult blood. The reaction to the serologic test for syphilis was negative.

Serum bilirubin was normal. Result of the thymol turbidity test was 2.4 units, zinc sulfate 16 units, cephalin flocculation test 1 plus in twenty-four and forty-eight hours. Bromsulfalein retention was 1 per cent in forty-five minutes. On admission the serum alkaline phosphatase was 6.4 Bodansky units. Subsequent determinations are noted in Figure 3. The serum total protein was 6.9 gm. per cent of which albumin was 57.8 per cent, alpha globulin 13.2 per cent, beta globulin 9.3 per cent and gamma globulin 19.7 per cent. SGOT was 14 units per ml. and SGPT 10 units per ml.

Serum iron was 30 μg. per cent and total iron-binding capacity 365 μg. per cent. Four hours after an oral dose of 240 mg. of ferrous gluconate the serum iron rose to 358 μg. per cent. Bone marrow and liver biopsy specimens were within normal limits. Results of a xylose absorption test and a water test (Soffer) for adrenal function were normal.

Roentgenograms of the long bones suggested the bone age to be six years. The heart appeared to be enlarged somewhat in the transverse diameter. Roentgenogram of the skull revealed osteoporosis.

Ten days after admission therapy with Ferrosan, one tablet three times a day, was started. Eleven days after the institution of oral iron therapy the hemoglobin was 6.6 gm. per cent, hematocrit 33 per cent and reticulocyte count 7 per cent. The patient had gained 4.5 pounds in four weeks, and 11 pounds after nine weeks. At that time the hemoglobin was 11.2 gm. per cent, hematocrit 41 per cent, serum iron 124 μg. per cent and total iron-binding capacity was 209. The alkaline phosphatase had increased to 19.6 Bodansky units but then fell to 12.2. (Fig. 3.) The liver and spleen were barely palpable.

The following three cases were observed at the Saadi Hospital, a unit of the Shiraz University Medical Center. It was not possible to study these patients as thoroughly as the preceding eight who were under our daily observation at the Nemazee Hospital. However, each presented the salient features of the syndrome described and thus is included in the series.

CASE IX. An eighteen year old boy (M. A.), was admitted to the hospital with the chief complaint of pallor and easy fatigability since childhood. He gave a history of geophagia of several years' duration. His diet was poor in animal protein. On admission the temperature was 37.3°C. His general appearance was that of a twelve year old boy. His weight was 33.6 kg. He had no pubic, axillary or facial hair. The external genitalia were small. The parotid glands were enlarged. Liver and spleen were enlarged. The hemoglobin on admission was 3.2 gm. per cent, the hematocrit was 15 per cent. Total leukocyte count was 3,800 per cu. mm. Serum total bilirubin was 0.7 mg. per cent. Total protein and paper electrophoresis were normal. The serum alkaline phosphatase was 10 Bodansky units. Result of the thymol turbidity test was 3 units, zinc sulfate turbidity test 12 units, cephalin flocculation test 1-plus in forty-eight hours. The serum iron was 78 μg. per cent.

Roentgenograms failed to show any evidence of esophageal varices. The bone age determined by roentgenogram was twelve years. Liver biopsy specimen showed slight fatty infiltration. A bone marrow biopsy specimen did not reveal any abnormalities.

The patient received oral iron therapy (Ferrosan, one tablet three times a day) for twenty weeks, and the hemoglobin rose to 12.4 gm. per cent. He gained 10 pounds of body weight. The patient was discharged from the hospital and it was not possible to follow his course after this date.

CASE X. A twenty-one year old man (M. A.), entered Saadi Hospital on October 15, 1958, complaining of weakness. He had been pale, tired easily and for seven years became short of breath on exertion. He also complained of having fever and chilly sensations at times. His father and two brothers were dead of an unknown cause. The mother is living and well. The patient's diet had consisted almost entirely of wheat bread, with occasional mast (yogurt) and dates. He stated that he never ate meat, eggs, fruits or vegetables.

Physical examination revealed a man with a wrinkled skin having the appearance of a twelve year old boy. He weighed 37.7 kg. There was marked pallor. He was dull and apathetic. The nails were spoon-shaped. The heart was enlarged, with a loud systolic murmur at apex. The lungs were clear. Examination of the abdomen revealed no ascites. The

liver was not palpable, but the spleen could be felt at the costal margin. There was no edema. Blood pressure was 130/40 and 115/45 mm. Hg on two observations. The testes and penis were the size of those in an immature boy. There was no facial, axillary or pubic hair.

The hemoglobin on admission was 3 gm. per cent, red blood cell count 1.56 million per cu. mm., white blood cell count was 9,200 per cu. mm. with normal differential. Marked poikilocytosis and anisocytosis was observed. Urinalysis was within normal limits.

The serum iron was 16 μg. per cent, total iron-binding capacity was 480 μg. per cent. Results of liver function tests revealed a serum total bilirubin of 1.10 mg. per cent. Bromsulfalein retention was 10 per cent after forty-five minutes; the serum alkaline phosphatase was 7 Bodansky units, SGOT 30 units, SGPT 10 units. Result of the thymol turbidity test was 2 units, zinc sulfate turbidity test 5 units. The serum total protein was 7.9 gm. per cent of which albumin was 54.8 per cent, alpha globulin 11.4 per cent, beta globulin 13.8 per cent, and gamma globulin 20.0 per cent. The prothrombin time was 100 per cent. A needle biopsy specimen of the liver showed no abnormalities.

Upon treatment with a high protein, high caloric diet, the patient's liver enlarged and ascites and edema developed. He was treated with ferrous sulfate and a reticulocytosis of 5 per cent was observed. Unfortunately, the patient could not be followed so the ultimate outcome is not known.

Comment: Even though we do not have adequate data or follow-up in this patient, nor did we enquire about geophagia since he was treated before we were aware that this might be an important feature, he is included because he had severe iron deficiency anemia, hypogonadism and dwarfism.

The results of the liver function tests were normal except for a bromsulfalein retention of 10 per cent on admission (which may have been related to cardiac failure). It is of interest that upon treatment with a nutritious diet ascites and an enlarged liver developed, which were presumed to be manifestations of the refeeding syndrome.

CASE XI. A twenty-one year old man (A. G.), was admitted with complaints of weakness, palpitation and pallor of the face. He gave a history of long-standing geophagia. The patient appeared much younger than his stated age. The face was pale and puffy. There was no facial, pubic or axillary hair. The external genitalia were underdeveloped. Both liver and spleen were enlarged.

On admission the hemoglobin was 3.9 gm. per cent and the hematocrit was 23 per cent. The serum iron was 25 μg. per cent. Bromsulfalein retention was 2.6 per cent in forty-five minutes, the serum bilirubin was normal. Results of the cephalin flocculation and thymol turbidity tests, serum proteins, SGOT, and SGPT were within normal limits. Roentgenograms of the chest, upper gastrointestinal series and skull were all within normal limits. A needle biopsy specimen of the liver was normal.

The patient was treated with oral iron (Ferrosan, one tablet three times a day) and in six weeks the hemoglobin was 12.1 gm. per cent and hematocrit was 46 per cent. The serum iron after iron therapy was 137 μg. per cent.

COMMENTS

This syndrome is characterized by marked hypochromic anemia due to iron deficiency, hepatosplenomegaly, dwarfism, lack of development of primary and secondary sexual characteristics, and a history of prolonged geophagia. In all cases the diet was markedly deficient in animal protein. In view of the dietary deficiency one might question whether there could be a relationship to protein malnutrition as described in Africa, Jamaica, India and other countries, and usually referred to as kwashiorkor [*2,3*]. However, the features of that disease include edema, skin and hair changes, with onset in infancy or early childhood, and fatal termination in many cases if untreated. None of these features were present in the cases reported herein, and the salient features of this syndrome are not expected in patients with protein malnutrition as reported from other countries. In addition to these differences the dietary pattern is also dissimilar since villagers in Iran eat large quantities of wheat, one of the best cereals in respect to both content and quality of protein (12.3 gm. per 100 gm. [*4*]), whereas patients in whom kwashiorkor develops consume a predominantly high carbohydrate diet which is low in protein, both animal and vegetable. Thus the only common denominator in these two syndromes is a low intake of *animal* protein.

In speculating on the pathogenesis of the hepatosplenomegaly seen in each of the cases a prominent possibility is fatty liver, since this is accepted as a usual feature in protein malnutrition [*2*]. Although four of the needle biopsy specimens revealed slight to moderate fatty infiltration, five biopsy specimens showed entirely normal liver histology. One patient had probable cirrhosis on biopsy, but results of all the liver function tests in this patient were within normal limits after he recovered from congestive heart failure which was believed to be caused by anemia alone. In another patient the biopsy specimen showed some fibrosis which could not be classified as cirrhosis of the liver. Thus in our

patients the histologic lesions in the liver varied considerably. Whether or not some would have gone on to cirrhosis if left untreated, cannot be answered. It is interesting that after several weeks of treatment with an adequate diet and oral iron therapy, which uniformly resulted in normal levels of hemoglobin, the liver and spleen both decreased markedly in size. This lends support to the probability that in our patients the hepatosplenomegaly was in some way related to severe anemia alone. It is known that such can occur, the explanation being obscure. Portal pressure was normal in the two patients in whom it was measured, and therefore one cannot invoke portal hypertension as a possible mechanism for splenomegaly.

In patients with the kwashiorkor syndrome hyperglobulinemia has been noted [*5*]. In our patients the protein electrophoretic patterns were essentially normal. Amongst the "liver function" tests, the only abnormality noted in some cases was increased level of the alkaline phosphatase in the serum. (As will be noted subsequently, we do not believe that this was a measure of liver function in these cases.)

We believe that the cirrhosis found on biopsy in one patient was a coincidental finding inasmuch as cirrhosis is a very common disease among the villagers of Iran.

The pathogenesis of the severe anemia present in all patients should next be considered. The laboratory and clinical findings, as well as the prompt response to treatment with iron in every case, left no doubt that it was an iron deficiency anemia.

In western countries it is most unusual to find iron deficiency anemia in patients who have neither blood loss nor intestinal malabsorption. In our patients neither of these factors could be demonstrated. The stool examinations failed to reveal evidence of chronic blood loss. No gastrointestinal lesions were found as a result of complete x-ray examinations. Hookworm infestation is not seen in this part of Iran nor did stool examinations reveal this or other parasites. However, moderate iron loss may occur through excessive sweating and skin desquamation from sunburn in a hot climate [*6,7*].

Intestinal absorption was normal as evidenced by xylose and iron absorption tests, as well as by a prompt hematologic response to oral iron therapy.

If one considers the iron requirements in these patients, the probable iron content of their diets, and certain other dietary factors bearing on iron absorption a reasonable explanation for iron deficiency can be found. Their usual diet consisted largely of wheat, which has an iron content of 3.4 mg. per 100 gm. [*4*]. However, this cereal also has a very high phosphorus content. Iron in food is much less well absorbed than iron salts in solution [*8*], and this is particularly true when the food contains a high phosphate content [*9*]. Thus one may presume that the iron contained in the wheat flour was not absorbed efficiently because of the formation of insoluble iron phosphate complexes. In addition to this factor there may well have been a partial vitamin C deficiency because the dietary histories revealed low intake of foods containing vitamin C. Vitamin C is important in promoting iron absorption by virtue of its being a reducing substance, converting ferric to ferrous iron; and perhaps by other poorly understood mechanisms.

Finally, the daily iron requirement of these patients who had not grown normally and were thus physiologically still children, probably was much higher than 1 mg. which is generally considered to be the requirement of an adult man.

The phenomenon of geophagia, present in nine of the patients, deserves mention. Many children in Iran eat clay in varying amounts for two or three years in early childhood. They seem to enjoy the taste and perhaps it satisfies hunger. Our patients, however, continued to eat clay for ten to thirteen years in large amounts and some had geophagia until admission to the hospital. According to a recent report, the caloric intake is poorer, with lower hemoglobin, in women who eat clay than in others [*10*]. It is a clinical impression among many Iranian physicians that severely anemic patients are likely to be clay eaters. It therefore seems possible that if geophagia is of long duration and of considerable degree the patients may suffer from severe anemia. Although the mechanism is not clear a high phosphate content of clay, and its possible chelating action, would tend to interfere additionally with iron absorption.*

* During the summer of 1960 a third year medical student, Mr. Peter Greenwald of State University of New York Medical Center in Syracuse, lived in a village of Iran of about 1,000 inhabitants, working under a Smith, Kine & French Foreign Fellowship. He made a special study of the phenomenon of geophagia, interviewing 171 patients. Seventy-eight of these had eaten dirt at some time in their lives, nearly all for brief periods either as children, or during pregnancy. He found no one in this village who had (1) a history of *prolonged* geophagia without this syndrome, or (2) the syndrome without a history of geophagia. He saw two patients with all features of the syndrome.

In all but one patient in whom gastric analysis was performed, achlorhydria was found. Presumably this was secondary to prolonged malnutrition and anemia [*11*]. However, it was not an inhibitory factor in iron absorption because all patients responded promptly to oral iron therapy. It is of interest that in three patients in whom gastric analysis was repeated after prolonged treatment, free acid still was not present.

The probable factors concerned in the mechanism of anemia may be summarized as follows: (1) the total amount of iron in the diet was probably insufficient over many years in respect to growth requirements; (2) the iron in the diet was largely unavailable for absorption because of an associated high phosphate content rendering it insoluble; (3) an accompanying deficiency of vitamin C may have been important; (4) excessive sunburn and sweating probably caused greater iron loss from the skin than would occur in a temperate climate. Geophagia may or may not be related to the anemia in some as yet undetermined manner.

In at least two patients congestive heart failure, due to severe anemia alone, was evident. They promptly recovered after improvement in the anemia associated with iron therapy.

Almost all patients had a low grade fever on admission and they became afebrile after about four weeks of iron therapy.

In one patient roentgenograms of the skull revealed changes compatible with thalassemia. However, similar changes have been recorded in chronic iron deficiency anemia [*12*].

Although our laboratory studies for endocrine dysfunction were not complete because of lack of facilities, there was no clinical evidence for panhypopituitarism, hypothyroidism or hypoadrenalism. Hypogonadism may have been either primary or secondary to lack of pituitary gonadotrophic hormone. The pituitary gland is known to be unusually susceptible to malnutrition, especially in relation to the gonadotropic and growth hormones [*13*]. Thus it is likely that both hypogonadism and dwarfism in the patients were caused by anterior pituitary failure related to malnutrition. It is of great interest that in four subjects who could be followed up after six to nine months, pubic hair appeared, with increase in size of penis and testes (Cases I, III, V and VI). This could only be related to the fact that the patients' anemia was corrected and they had received a nutritious and balanced diet, with consequent weight gain.

The serum alkaline phosphatase was elevated in ten cases (not measured in Case XI). This elevation seems to have been associated with the patient's receiving a normal diet for some time because it rose markedly in the three cases in which it was determined repeatedly, starting with admission. Those patients whose alkaline phosphatase level was elevated on admission to this hospital had been in Saadi Hospital for two to three weeks before transfer, where they had been given a normal diet. Figure 3 shows the increasing values for this enzyme with a later fall, as clearly demonstrated in Cases III, VII and VIII, associated with hospitalization. The prolonged increase above normal, noted in all patients studied, suggests that this might be associated with bone growth. However, the values obtained were much higher, in many instances, than would occur in normal growing children.

In one patient we were able to have the serum zinc determined.* This was distinctly low (71 μg. per cent; normal range in 100 to 140). The zinc content of almost all foodstuffs parallels that of their iron content [*13*]. Inasmuch as heavy metals may form insoluble complexes with phosphates one may speculate that the factors responsible for lack of iron absorption in these patients also governed the absorption of zinc. This could account for the low serum zinc level found in this patient. Zinc deficiency in rats results in irreversible testicular atrophy [*14*]. Other manifestations of zinc deficiency in the mouse, rat and hog include lack of growth and retardation of skeletal maturation. Changes in alkaline phosphatase (a zinc-containing enzyme) have also been observed in hogs with zinc deficiency. Increasing activity of this enzyme has been noted when zinc-deficient animals received increased amounts of dietary zinc [*14*]. In the cases described herein, dwarfism, testicular atrophy, retardation of skeletal maturation and changes in serum alkaline phosphatase might be explained on the basis of zinc deficiency. Although the serum zinc level could be obtained in only one patient, the low result obtained, when added to secondary supporting evidence (i.e., increased alkaline phosphatase), appears to justify serious consideration of this hypothesis.

Inconclusive evidence is present in the litera-

* Through the courtesy of Dr. W. E. C. Wacker and Dr. Bert L. Vallee, Peter Bent Brigham Hospital, Boston, Massachusetts. Samples from several other patients were sent air mail to Boston for zinc determinations but were unfortunately either lost or spoiled in transit.

ture that primary nutritional human zinc deficiency may have been present in Chinese subjects with nutritional edema and semi-starvation [*14*].

The entire clinical picture, therefore, could be explained if one postulates that these patients had severe iron and zinc deficiency. Vitamin A-resistant night blindness of subjects afflicted with postalcoholic cirrhosis of the liver has been attributed to inactivity of alcohol dehydrogenase (a zinc-containing enzyme). Two of our patients had night blindness without other signs of fat-soluble vitamin deficiency and zinc deficiency may have been the causative factor. A high concentration of zinc in the male reproductive tract has been noted [*14*]. The female genital tract does not exhibit such unusual zinc concentration. This may explain the fact that all of our patients who show the manifestations of this syndrome are males. We have seen no females with this clinical picture.

Low serum zinc concentration has been reported in patients with severe liver disease and usually correlates well with its severity [*15*]. We found no evidence that our patients had severe liver disease to account for a possible zinc deficiency.

In most cases the history revealed that other siblings were perfectly normal. It is difficult to understand why only one or two members in the family suffered from this syndrome, presumably an effect of malnutrition, since all members of the family would consume the same diet. As far as we could determine, it appeared that those who suffered were the ones who ate clay for many years. Whether or not geophagia played an important role in preventing absorption of iron and zinc, thus causing this clinical picture, cannot be ascertained at present. Nonetheless this does seem to be a possibility and only further investigations can throw light on this aspect.

Reimann [*1*] considers that a genetic defect might explain certain aspects of the picture here presented. However, he believes that iron deficiency in the mother damages the sequence of differentiation, leading to developmental anomalies of the skeleton particularly. Thus, both he and we are apparently in agreement that malnutrition is the basic cause of the syndrome.

Although the incidence and significance of geophagia in the population have not been adequately studied, this appears to be one common denominator among the group presented. Further information relative to this aspect is now being sought.

SUMMARY

A syndrome occurring in males, characterized by severe iron deficiency anemia, hypogonadism, dwarfism, hepatosplenomegaly and geophagia, has been observed in villagers in Iran suffering from malnutrition. Eleven such patients, studied in detail, are described.

Despite hepatosplenomegaly, results of the liver function tests were uniformly normal except for the serum alkaline phosphatase, which was consistently elevated.

The anemia was not associated with blood loss, hookworm infestation or intestinal malabsorption, and responded promptly to oral iron therapy. Although the diet contained adequate amounts of iron it is believed that the predominantly wheat diet, with its high phosphate content, interfered with absorption because of the formation of insoluble iron complexes. Correction of the anemia resulted in marked decrease in the size of the liver and spleen.

Prolonged follow-up of patients receiving a well balanced diet indicates that the endocrine abnormalities of growth and sexual development are reversible.

The relationship of geophagia (which occurred in nearly all patients) to this syndrome is not clear, and is discussed.

The possibility of zinc deficiency is considered as an explanation of hypogonadism, dwarfism and changes in alkaline phosphatase.

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A Comparison of Laboratory Methods for the Control of Anticoagulant Therapy with Prothrombinopenic Agents*

I. The Quick One-Stage Procedure, the Prothrombin and Proconvertin Test and the One-Stage Determination of True Prothrombin Activity

THEODORE RODMAN, M.D., BERNARD H. PASTOR, M.D. *and* KENNEDY C. FAWCETT, M.D.†
Philadelphia, Pennsylvania

FOR nearly two decades the Quick one-stage procedure for the determination of prothrombin complex activity, or one of its modifications, has been widely used for the laboratory control of anticoagulant therapy with prothrombinopenic drugs. The Quick test measures the time needed for the thrombin titer of plasma to reach the clotting level in the presence of a fixed amount of thromboplastin and calcium. This is influenced by the concentration of prothrombin (factor II) in the plasma, and also varies with the amount of proaccelerin (factor V), proconvertin (factor VII) and probably Stuart-Prower factor (factor X). A low "prothrombin time" may therefore reflect a deficiency of any or all of these clotting factors.

By addition to the clotting system of a reagent containing all the clotting factors but one, a deficiency of that factor alone may be measured. In the same way the use of a reagent deficient in two of the factors will measure the level of both factors in the test plasma. More complex tests applying this principle have been recommended for clinical use, and the proponents of each claim for it a distinct superiority over the Quick procedure. Because of the relative simplicity of the Quick test and the fact that it is the standard procedure in most clinical laboratories, a study was undertaken to determined whether any of these newer tests would really provide smoother, more effective anticoagulant therapy, with a reduced incidence of thrombotic episodes and hemorrhagic complications.

MATERIAL AND METHOD

Four tests of the clotting mechanism, namely, the Link-Shapiro modification of the Quick one-stage technic using Simplastin,®‡ the Link-Shapiro modification of the Quick one-stage technic using Acuplastin,®‡ the P and P test of Owren [*1*]§ and the determination of the true prothrombin activity by the one-stage technic of Owren and Aas [*2*], were performed serially in 107 patients requiring anticoagulant therapy. Each patient was randomly assigned to one of four groups, and the anticoagulant therapy of the members of each group was controlled by one of the four tests. (Table I.) All four tests were performed in each patient daily until a stable maintenance dose of anticoagulant was established and the frequency of testing was then reduced to three times weekly. The results of the tests were reported in seconds and converted to per cent plasma activity by reference to a curve based on imidazole saline buffer dilution of pooled normal plasma. Twenty-four patients were controlled by the results of the Quick one-stage procedure using Simplastin, twenty-seven by the Quick one-stage procedure using Acuplastin, thirty-one by the P and P test and twenty-five by the determination of true prothrombin activity. (Table I.) All patients were treated with bishydroxycoumarin (dicumarol)

‡ Simplastin was very kindly provided for this study by Warner-Chilcott Laboratories, Morris Plains, New Jersey, and Acuplastin by Dr. H. O. Singher, Ortho Research Foundation, Raritan, New Jersey.

§ A slight modification of this test was employed. Oxalated plasma was used, and a 1:5 dilution was substituted for the 1:10 dilution recommended by Owren. This was necessary for convenience since excessively long plasma clotting times were obtained with the greater dilution using Acuplastin as our tissue thromboplastin.

* From the Department of Medicine and The Medical Research Laboratories, Veterans Administration Hospital, Philadelphia, Pennsylvania. Manuscript received December 27, 1960.
† Present address: U. S. Naval Hospital, Great Lakes, Illinois.

TABLE I
NUMBER OF CASES AND DIAGNOSES

Diagnosis	Patients (no.)	Average Age (yr.)	Duration of Treatment (average no. days)
Quick Test with Simplastin (Twenty-four Patients)			
Myocardial infarction	12	55	37
Pulmonary infarction	4	51	22
Thrombophlebitis	3	43	37
Embolism	1	36	14
Miscellaneous	4	56	26
Quick Test with Acuplastin (Twenty-seven Patients)			
Myocardial infarction	13	58	35
Pulmonary infarction	3	47	19
Thrombophlebitis	4	48	36
Embolism	2	59	39
Miscellaneous	5	49	66
P and P Test (Thirty-one Patients)			
Myocardial infarction	12	57	40
Pulmonary infarction	4	60	37
Thrombophlebitis	6	50	25
Embolism	4	50	46
Miscellaneous	5	48	21
True Prothrombin Test (Twenty-five Patients)			
Myocardial infarction	14	56	29
Pulmonary infarction	3	53	32
Thrombophlebitis	4	41	16
Embolism	1	71	32
Miscellaneous	3	68	14

alone unless a specific indication (such as acute pulmonary embolism) was present for the use of heparin during the induction period. An attempt was made to maintain patients in a therapeutic range of 10 to 30 per cent with each test.

RESULTS

Pretreatment Level of Plasma Activity. There was wide variation in the control level of plasma activity measured by each of the four tests before the administration of the anticoagulant.

Eighty-nine per cent of the patients had a true prothrombin level in the normal range (above 60 per cent) initially, 79 per cent were in the normal range with the P and P test, 75 per cent with the Quick test using Simplastin, and only 35 per cent with the Quick test using Acuplastin. (Table II.) The highest values were obtained with the true prothrombin test, with an average of 87 per cent. Intermediate average values of 77 per cent for the P and P test and 67 per cent for the Quick test with Simplastin were obtained, and the lowest values were found with the Quick test using Acuplastin, the average being 54 per cent. (Table III.) The mean difference in activity between the true prothrombin level and the Quick one-stage determination using Acuplastin was 32 for the group, and in many cases the true prothrombin level was above 80 per cent while the Acuplastin level was below 40 per cent.

Induction Therapy. When induction of anticoagulant therapy with bishydroxycoumarin was accomplished by our standard method using a large single dose (approximately 600 mg.) followed by an arbitrary maintenance dose (approximately 100 mg.) on the second day, the true prothrombin value did not drop below the therapeutic range (less than 10 per cent) within sixty-four hours in any of the patients, the result of the Quick test with Simplastin was below the therapeutic range in only seven patients (13 per cent), but the P and P test showed values below 10 per cent in thirty-four patients (61 per cent) and the Quick test with Acuplastin in thirty-two patients (57 per cent). (Table IV.) By this time values in twenty-seven patients (48 per cent) had not yet reached the therapeutic range of the true prothrombin test. In only three patients (5 per cent) were values still above 30 per cent with the Simplastin test, in two (4 per cent) with the P and P test and in two (4 per cent) with the Acuplastin test. An average of 3.3 days was required to reach the therapeutic range of the true prothrombin test, 2.3 days for the Simplastin test, 2.2 days for the P and P test and 1.9 days for the Acuplastin test. In many individual cases the plasma activity measured by the Acuplastin test, the P and P test and the Simplastin test had been in the therapeutic range from two to four days before the true prothrombin level was depressed below 30 per cent.

Maintenance Therapy. Activity in patients whose anticoagulant was prescribed according to the results of the Quick test using Acuplastin was in the therapeutic range 84 per cent of the time, by the Quick test using Simplastin 81 per cent of the time, by the true prothrombin test 81 per cent of the time and by the P and P test only 72 per cent of the time. (Table V.) Episodes of

TABLE II
PRETREATMENT LEVEL OF PLASMA ACTIVITY

Test of Clotting Mechanism	Patients with Per cent Plasma Activity of											
	20–39		40–59		Total below 60		60–79		80–100		Total above 60	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
True prothrombin	0	...	6	11	6	11	7	13	40	76	47	89
P and P test	0	...	12	21	12	21	17	30	28	49	45	79
Quick test with Simplastin	5	5	19	20	24	25	40	41	23	24	73	75
Quick test with Acuplastin	11	19	27	46	38	65	16	27	5	8	21	35

TABLE III
AVERAGE PRETREATMENT LEVEL OF PLASMA ACTIVITY

Test of Clotting Mechanism	Per cent of Normal
True prothrombin	87
P and P test	77
Quick test with Simplastin	67
Quick test with Acuplastin	54

escape from the therapeutic range or excessive hypoprothrombinemia occurred at a frequency of 4.7 per hundred patient days of therapy in the group managed by the P and P test, 3.5 by the Simplastin test, 3.1 by the Acuplastin test and 2.9 by the true prothrombin test. (Table VI.) A total of 115 such escapes occurred.

The average maintenance dose of bishydroxycoumarin in the four groups of patients was nearly identical. (Table VII.)

The serial values obtained with the four tests in each patient during maintenance therapy were in close agreement in forty-two of the 107 patients, the difference between the test showing the highest and lowest value being less than 5 per cent. The results in one such patient are illustrated in Figure 1. In the other sixty-five patients small but fairly consistent differences were observed. Most often, the true prothrombin was highest (60 per cent of the time), the Simplastin value second, the Acuplastin value third and the P and P value lowest (86 per cent of the time). (Table VIII.) The greatest difference encountered between a test showing the highest value and one showing the lowest value was 15 per cent, the average difference being 9 per cent. As a result of this small range of values among the four tests,

TABLE IV
RESULTS OF INDUCTION THERAPY WITH A SINGLE LARGE DOSE OF BISHYDROXYCOUMARIN

Test of Clotting Mechanism	Patients with Per cent Plasma Activity within Sixty-four Hours						Average No. of Days to Reach Therapeutic Range
	Below 10		10–30		Above 30		
	No.	%	No.	%	No.	%	
True prothrombin	...	...	29	52	27	48	3.3
Quick test with Simplastin	7	13	46	82	3	5	2.3
P and P	34	61	20	35	2	4	2.2
Quick test with Acuplastin	32	57	22	39	2	4	1.9

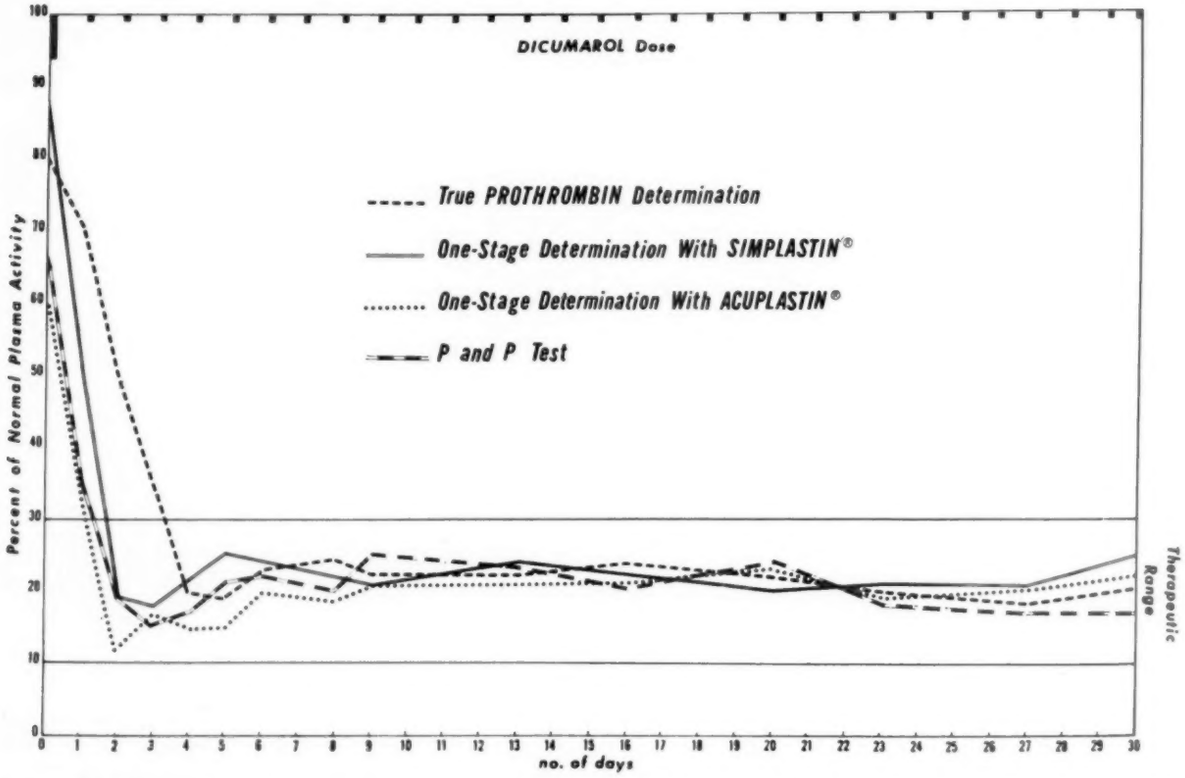

FIG. 1. Serial determinations expressed as per cent of normal activity during thirty days of anticoagulant therapy with bishydroxycoumarin. Values for the true prothrombin determination, P and P test, Quick one-stage determination with Simplastin and with Acuplastin are in close agreement except for a slight lag in the initial fall of the true prothrombin level.

values in most patients maintained in the middle of the therapeutic range (around 20 per cent) with one of the tests were also within the therapeutic range (between 10 and 30 per cent) with the other three tests. This was particularly true of the patients in whom activity was controlled by the Quick test with either Simplastin or Acuplastin since the values for these two tests were usually intermediate between those of the true prothrombin and the P and P test. In some cases, however, values controlled in the therapeutic range 100 per cent of the time with the true prothrombin test might occasionally be in the hypoprothrombinemic range (below 10

TABLE V
MAINTENANCE THERAPY

Test of Clotting Mechanism	Days in Therapeutic Range		Days Out of Therapeutic Range	
	No.	%	No.	%
Quick test with Acuplastin	834	84	159	16
Quick test with Simplastin	526	81	123	19
True prothrombin	447	81	105	19
P and P	728	72	280	28

TABLE VI
MAINTENANCE THERAPY
FREQUENCY OF ESCAPE FROM THERAPEUTIC RANGE
(PER 100 PATIENT DAYS OF THERAPY)

Test of Clotting Mechanism	Per cent of Plasma Activity		Total
	Above 30	Below 10	
P and P	2.9	1.8	4.7
Quick test with Simplastin	2.0	1.5	3.5
Quick test with Acuplastin	1.9	1.2	3.1
True prothrombin	2.2	0.7	2.9

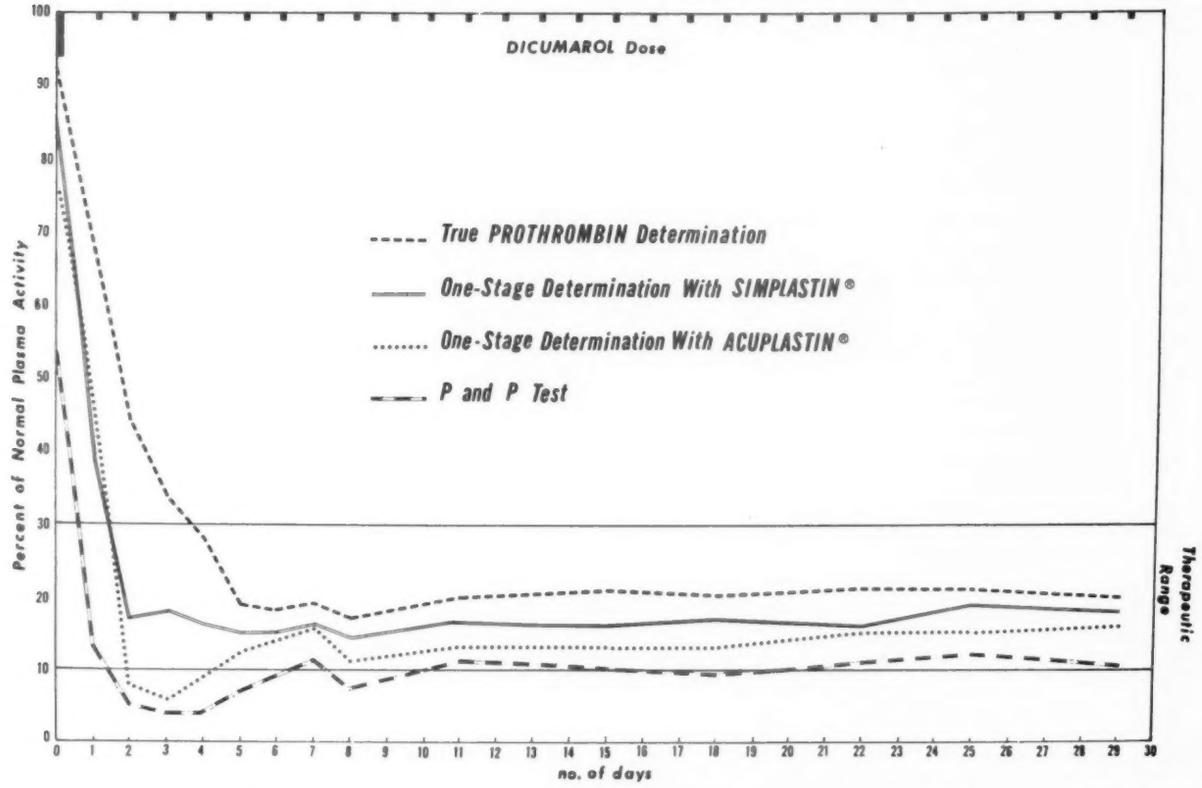

FIG. 2. Serial determinations expressed as per cent of normal activity during twenty-nine days of anticoagulant therapy with bishydroxycoumarin controlled by the values of the true prothrombin determination. Values for the Quick one-stage determination with Simplastin remain in the therapeutic range, but values for the Quick test with Acuplastin and the P and P test are low and occasionally below the therapeutic range.

per cent) according to the P and P test (Fig. 2), or values controlled in the therapeutic range 100 per cent of the time by the P and P test might occasionally have undesirably high plasma activity as judged by the true prothrombin determination. (Fig. 3.)

Termination of Anticoagulant Therapy. No significant difference was observed among the four tests in the rate of return to normal levels of plasma activity after termination of anticoagulant therapy. An average of 4.5 days was required to reach 50 per cent with each test.

Complications. Only four hemorrhagic episodes were encountered in this series; none of the patients had thromboembolic complications during therapy. In two patients results of all the tests at the time of bleeding showed plasma activity of less than 10 per cent. In one patient the P and P and Acuplastin values were less than 10 per cent, the Simplastin value was 11 per cent and the true prothrombin value was 19 per cent. In the fourth patient both the P and P and Acuplastin values were below 10 per cent, the Simplastin value was 12 per cent and the true prothrombin 17 per cent.

COMMENTS

The clinical value of the Quick one-stage test for prothrombin complex activity in the control of anticoagulant therapy has been questioned by several investigators. Owren [*1*] is of the opinion that the Quick test is insensitive and erratic. He devised another test of prothrombin and proconvertin activity (P and P test) in which a

TABLE VII
AVERAGE MAINTENANCE DOSE (MILLIGRAMS OF BISHYDROXYCOUMARIN)

Test of Clotting Mechanism	Range	Average
Quick test with Acuplastin	32–94	61
True prothrombin	25–125	60
Quick test with Simplastin	30–100	59
P and P	21–130	57

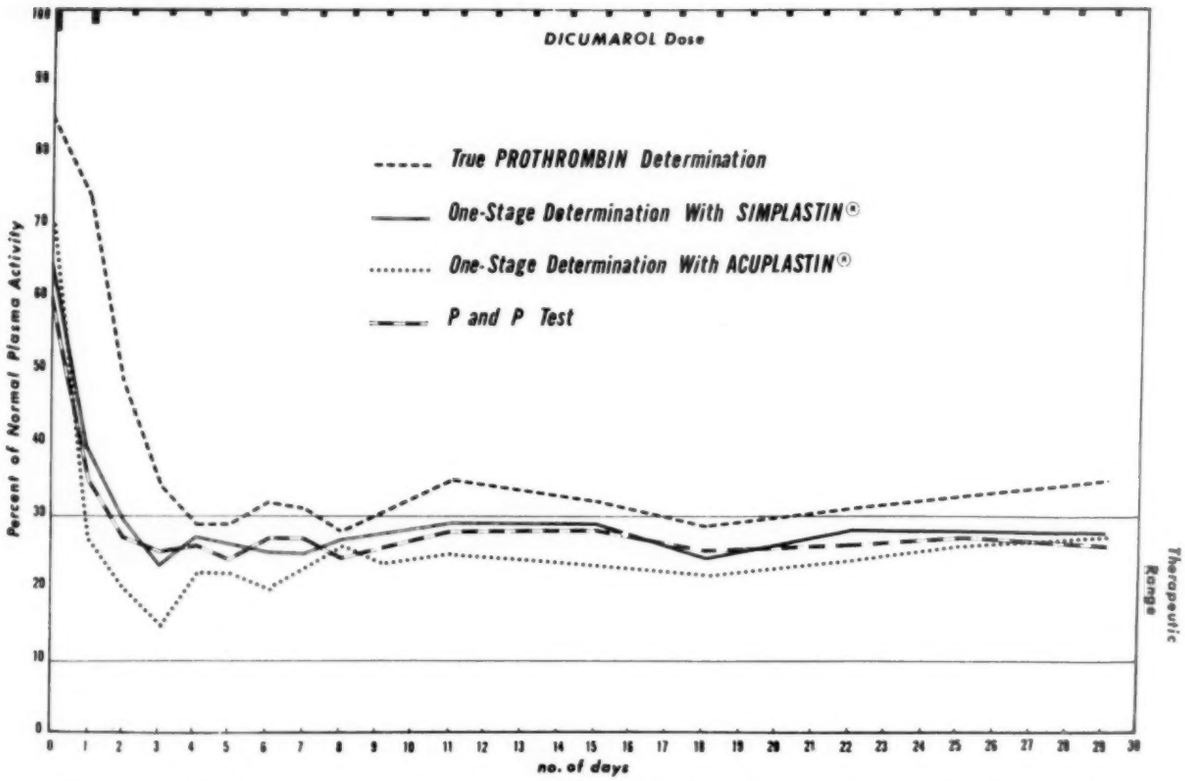

FIG. 3. Serial determinations expressed as per cent of normal activity during twenty-nine days of anticoagulant therapy with bishydroxycoumarin controlled by the values of the P and P test. Values for the Quick one-stage determination remain in the high therapeutic range, but values for the true prothrombin determination are frequently above the therapeutic range.

tenfold dilution of the test plasma is designed to increase sensitivity, and barium sulfate-adsorbed plasma is added as a source of factor v (proaccelerin) and fibrinogen to avoid prolongation of clotting time during the test by a deficiency of these factors in the patients' plasma. More recently Owren [3] has introduced a newer test for plasma clotting factors, the Thrombotest which is now being evaluated in our laboratory. Sise and his associates [4] object to the Quick one-stage test because of its sensitivity to changes in factor VII (proconvertin) activity, and its relative insensitivity to true prothrombin activity, which they consider to

TABLE VIII

COMPARISON OF PLASMA ACTIVITY VALUES IN SIXTY-FIVE CASES SHOWING SIGNIFICANT DIFFERENCES

Test of Clotting Mechanism	Frequency with which value was							
	Highest		Second		Third		Lowest	
	No.	%	No.	%	No.	%	No.	%
True prothrombin	39	60	24	37	2	3	...	...
Quick test with Simplastin	26	40	27	42	12	18	...	...
Quick test with Acuplastin	...	...	14	21	42	65	9	14
P and P test	...	...	...	...	9	14	56	86

correlate best with bleeding and thrombosis. Although Sise and his co-workers find the Quick test too sensitive to changes in factor VII activity, others [5] have criticized it for insensitivity to this same factor which they say may permit reduction of factor VII to dangerous levels undetected by the test. They attribute this to the fact that most commercial thromboplastins contain factor VII-like activity, and suggest the use of a thromboplastin preparation relatively free of this activity. Still other investigators [6] have suggested abandonment of all of these tests in favor of a modification of the clotting time to measure the over-all coagulability of the blood. Hicks and Bonin [7], on the other hand, found that the Quick one-stage test correlated well with an assay of the entire group of "thromboplastic factors" affected by anticoagulants and concluded that it was a satisfactory although not ideal clinical test for anticoagulant control.

The present study was undertaken to assess, if possible, the validity of some of the objections to the standard Quick one-stage procedure as they apply to clinical practice. The Quick test performed with a standard commercial thromboplastin, Simplastin, and a thromboplastin reported to be free of factor VII activity, Acuplastin, was compared with the P and P test and the true prothrombin determination. An evaluation of the Mayer [6] modification of the clotting time was included in the study at first, but then eliminated because the time required for the test appears to make it unsuitable for routine clinical use in hospitalized patients.

Unfortunately, the fundamental question as to which factor or factors it is most important to regulate for effective anticoagulation remains unanswered. So too does the question as to which factor, when depressed, results in undesirable bleeding. Verstraete, Clark and Wright [5] believe that a deficiency of factor VII may lead to bleeding without a striking decrease in prothrombin, and that control of this factor is essential. Sise and his associates [4], on the other hand, believe that bleeding correlates well with the prothrombin concentration and poorly with the Quick test. In their report, however, the results of the Quick test were given in seconds and the true prothrombin determination converted to per cent, which makes comparison difficult. In addition to this the number of cases is small and it is doubtful whether a significant difference is present in the accuracy of the two tests in predicting hemorrhage or thrombosis. Hicks and Bonin [7] have observed that hemorrhage sometimes did not occur when all factors, including prothrombin, were reduced to immeasurably low levels, and that some patients bled at apparently safe levels. They postulated that hemorrhage may depend upon some vascular factor or other unknown factor rather than being solely dependent upon any single component or group of components in the clotting mechanism. Our clinical observations have shown that although many patients have an early fall in prothrombin complex activity to below 10 per cent, particularly those patients controlled by a test sensitive to deficits in factor VII, bleeding does not occur in the first week or ten days of anticoagulant therapy. On the other hand, bleeding in the later days of anticoagulant therapy is frequently observed in patients with values in the therapeutic range.

Lacking exact knowledge of the factor or factors which should be most carefully regulated in clinical anticoagulant therapy, we can only determine which of the available tests offers the most practical way of regulating those factors which are generally regarded as important in clinical anticoagulation. It is known that bishydroxycoumarin and related compounds reduce levels of factor II (prothrombin), factor VII (proconvertin), factor IX (plasma thromboplastin component) and factor X (Stuart-Prower factor). The wide disparity in the results of the four tests performed in each patient in this study before the administration of any anticoagulant suggests at once that different aspects of the clotting mechanism are being measured. When anticoagulant therapy was begun the precipitous drop in the values with the P and P test and the Quick test using Acuplastin appear to reflect the prompt depression of factor VII activity to which these tests are very sensitive. It is apparent that patients regulated by a test sensitive to factor VII activity will be given smaller doses of anticoagulant and, at least in the early days of therapy, will be carried at levels of prothrombin complex activity higher than those we are at present accustomed to consider therapeutic. It is not known whether this is desirable, but it does not appear to be any safer than the present method in which bleeding is rarely if ever observed in the first week even with very low levels. The true prothrombin values lag considerably behind but there is really no good evidence to indicate that anticoagulation is not effective during the period before the true prothrombin level is depressed.

Sise has observed that depression of factor x (Stuart-Prower) lags behind in a similar fashion. The significance of this is not clear since the role of this factor in clinical anticoagulant therapy or anticoagulant-induced hemorrhage is not understood. Its measurement is too difficult for routine clinical testing at present. The Quick test with Simplastin appears to give intermediate results. This would be anticipated, since it reflects factor VII activity but is less sensitive to it than either the P and P test or the Quick test with Acuplastin.

The results of this study do not support the contention that anticoagulant therapy is managed more smoothly and conveniently by any of the newer methods that have been suggested. The P and P test, because of its greater sensitivity, resulted in less stable control and more adjustment of dosage than the other three tests. Episodes of escape were somewhat more frequent with this test than with the others. A total of 115 escapes were observed during the study, and examination of the values of all four tests during the several days before such escapes does not suggest that the results of one of the tests will more easily predict or avoid such episodes than another.

It should be pointed out further that while the various tests purport to measure different factors, there appears to be considerable overlapping, even in methods used for the determination of a single factor, depending upon the exact technic employed. For example, the one-stage test for prothrombin activity gives results which are not comparable to those of the two-stage test, and obviously reflects depression of some factor or factors other than prothrombin alone. In addition, even in the performance of the same test, variations in reagents give wide disparity in the values obtained at different times.

In the light of our results it might seem difficult to explain the apparent superiority of more complex tests of the clotting mechanism over the Quick test in some of the earlier studies. The explanation may be that there are many pitfalls in the performance of the Quick test which lead to wide discrepancies in the results obtained in different clinical laboratories [*8*]. In comparing the efficiency of other tests to the Quick procedure care must be taken that the tests are performed concurrently, with comparable technic and preferably by the same person. When compared in this manner the apparent advantages are either small and insignificant or nonexistent.

SUMMARY

Several newer, more complex tests of the clotting mechanism have been suggested to replace the relatively simple Quick one-stage test for prothrombin complex activity.

In a controlled study of the P and P test, the one-stage determination of true prothrombin activity and the Quick one-stage test using two commercially available tissue thromboplastins, neither of the more complex procedures was shown to be superior to the Quick procedure. Because of the intermediate sensitivity of the Quick test, patients whose prothrombin complex activity values were controlled with it most often had values in the therapeutic range of the other two tests as well.

The Quick one-stage procedure, properly performed, appears to be a satisfactory method for the control of anticoagulant therapy in the light of our incomplete knowledge of anticoagulant mechanisms.

Acknowledgment: We wish to express our appreciation for the technical assistance of Mrs. Bertha L. Hoxter and Mrs. Esther H. Wolfe.

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II. Problems Encountered in the Laboratory Control of Anticoagulant Therapy with the One-Stage Determination of Prothrombin Complex Activity*

THEODORE RODMAN, M.D., BERNARD H. PASTOR, M.D. *and* BERTHA L. HOXTER, B.S.
Philadelphia, Pennsylvania

THE Quick one-stage determination of prothrombin complex activity, probably the most widely used test for the control of anticoagulant therapy with prothrombinopenic drugs, has not always proved entirely satisfactory in clinical practice. It has been said to be insensitive and erratic, and the results in different laboratories, and even in the same laboratory at different times, are not comparable. Other, usually more complex, procedures have been suggested to replace it, but in a controlled study in our laboratory none of these appeared to be superior to the Quick procedure [*1*]. It seemed worthwhile, therefore, to evaluate the sources of error in performance of the Quick test to determine why it has been found unsatisfactory, and how the troublesome discrepancies between results obtained in a single laboratory or in different laboratories might be eliminated.

MATERIALS AND METHOD

The study involved two phases, an evaluation of the effect of variations in technic on the prothrombin-complex activity determination in our laboratory, and a comparison of the results obtained on identical plasma specimens by fourteen different hospital clinical laboratories.

The variations in technic investigated in our laboratory included the following:

(1) *Comparison of Different Thromboplastin Preparations.* In the plasma of fifteen patients receiving anticoagulants, the prothrombin complex activity was determined by the Link-Shapiro modification of the Quick one-stage technic, using each of six tissue thromboplastins. The thromboplastins investigated were bacto-aplastin (a lung extract), bacto-thromboplastin, calsoplastin and a "home-made" thromboplastin (brain extracts), and Simplastin® and Acuplastin® (mixtures of brain and lung extract).† The determinations were made in triplicate and the values for each sample coincided within 5 per cent. The results were reported in seconds and converted to per cent of normal plasma activity by reference to a curve based on imidazole saline buffer dilution of pooled plasma from five to ten normal donors.

(2) *Comparison of Different Vials of the Same Thromboplastin Preparation.* The prothrombin complex activity was determined by the Link-Shapiro modification of the Quick one-stage technic in six patients receiving anticoagulants, using three vials each of Simplastin and Acuplastin selected at random from the same lot. The determinations were made in triplicate and the results for each sample coincided within 5 per cent.

(3) *Comparison of Dilution Curves Prepared with Different Diluents.* Using pooled plasma from five to ten normal donors, serial dilutions were made with 0.85 per cent saline solution, imidazole saline buffer, barium sulfate-adsorbed beef plasma and barium sulfate-adsorbed human plasma. The prothrombin complex activity of each dilution was determined by the Link-Shapiro modification of the Quick one-stage technic using two thromboplastin preparations, Simplastin and Acuplastin.

(4) *Variations in the Handling of Plasma Before Measurement of Plasma Activity.* The plasma of both normal subjects and patients receiving anticoagulants was used. The prothrombin complex activity was determined at once, using both Simplastin and Acuplastin, and serial determinations of plasma activity were performed on the same plasma after variable handling which included the use of refrigerated and non-refrigerated centrifuges, storage of plasma at room

† Simplastin was very kindly provided for this study by Warner-Chilcott Laboratories, Morris Plains, New Jersey and Acuplastin by Dr. H. O. Singher, Ortho Research Foundation, Raritan, New Jersey.

* From the Medical Research Laboratory of the Veterans Administration Hospital, Philadelphia, Pennsylvania.
Manuscript received December 27, 1960.

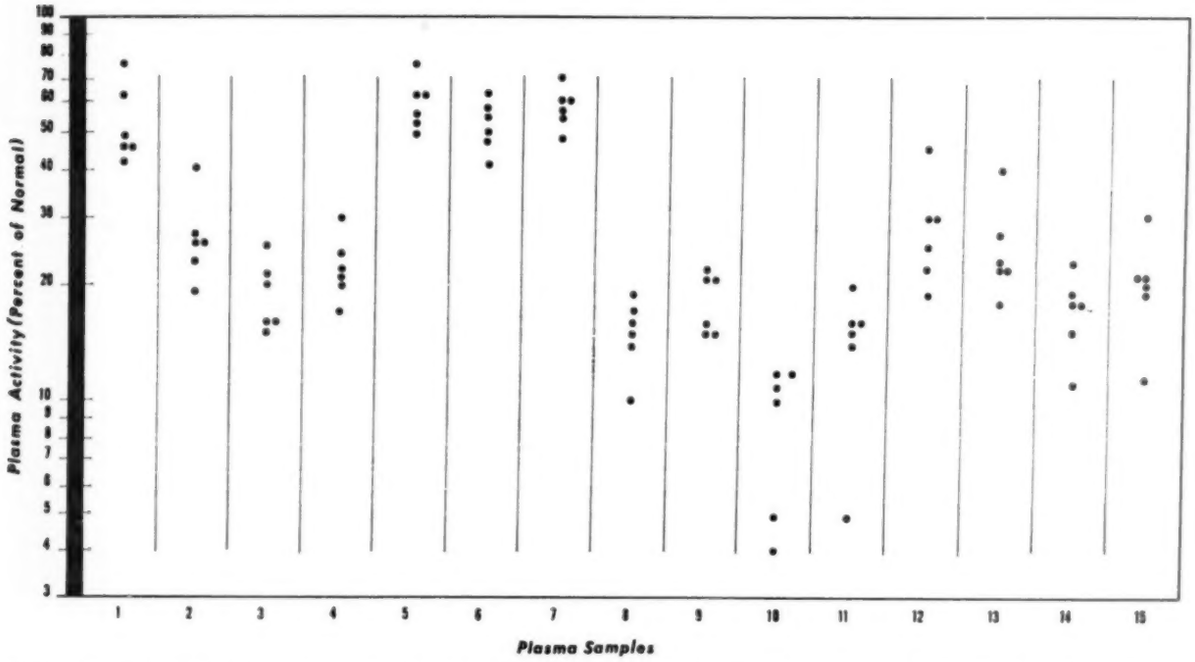

FIG. 1. Wide variations in prothrombin complex activity measured by identical technic but with different tissue thromboplastin preparations.

temperature or in the refrigerator for varying periods of time up to twenty-four hours, and exposure of the plasma to water bath temperature of 37°C. for periods from five to forty-five minutes.

In the second phase of the study the results of fourteen hospital laboratories were compared. To each laboratory we submitted a 2 ml. sample of the plasma of each of ten patients receiving anticoagulants. The specimens were delivered within two hours and each laboratory determined the prothrombin complex activity by the Quick one-stage technic. In addition to the report in seconds and per cent activity, each cooperating laboratory answered a questionnaire regarding the details of its technic.

TABLE I
VARIATIONS IN PROTHROMBIN COMPLEX ACTIVITY WITH DIFFERENT THROMBOPLASTINS

Plasma Sample	Highest Value (H) (%)	Lowest Value (L) (%)	Ratio (H/L)
1	75	42	1.8
5	75	50	1.5
6	63	41	1.5
7	80	48	1.7
Average	...	...	1.6
2	40	19	2.1
3	25	15	1.7
4	30	17	1.8
8	19	10	1.9
9	22	15	1.5
10	12	4	3.0
11	20	5	4.0
12	45	19	2.4
13	40	18	2.2
14	23	11	2.1
15	30	12	2.5
Average	...	...	2.3

RESULTS

Comparison of different thromboplastin preparations revealed marked variations in the values obtained for the same plasma specimen. (Fig. 1.) The differences were least in plasma samples showing nearly normal prothrombin complex activity (samples 1, 5, 6 and 7) and greatest in the plasmas with the most reduced activity (samples 10 and 11). In the first group of samples, with mean prothrombin complex activity above 50 per cent, the ratio between the highest and lowest values obtained in each plasma ranged from 1.5 to 1.8 with an average of 1.6. Among the remaining eleven samples, with a mean activity of 21 per cent, the ratio between the highest and lowest values obtained in each plasma ranged from 1.5 to 4 with an average of 2.3. (Table I.) The most striking differences were found between values obtained with bactothromboplastin, a brain extract, and bactoaplastin, a lung extract. With these two reagents

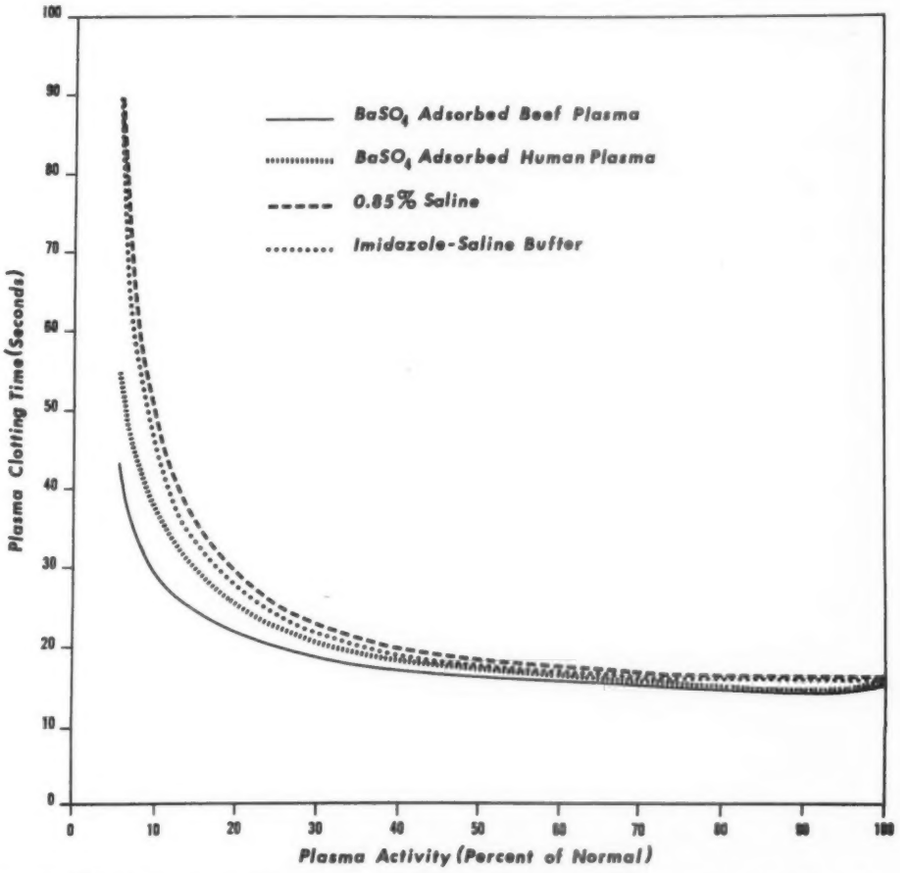

FIG. 2. Dilution curves obtained with 0.85 per cent saline solution and imidazole saline buffer are in fairly close agreement, but those obtained with barium sulfate-adsorbed plasma are displaced significantly to the left.

there was wide variation in the plasma clotting time of the patients receiving anticoagulants, even though the values for pooled normal plasma were almost identical (13.8 seconds and 13.2 seconds, respectively). The difference was most marked in the plasma samples with the least prothrombin complex activity, and the time for the lung preparation (bacto-aplastin) was consistently more prolonged than for the brain preparation (bacto-thromboplastin). Similar discrepancies have been observed by other investigators [*2–6*].

When different vials of the same tissue thromboplastin were compared, both Simplastin and Acuplastin were found to be well standardized within a single lot. The average deviation of a single determination from the average of all determinations with Simplastin was 5.9 per cent and with Acuplastin 8.4 per cent. This variation is not clinically significant although it is somewhat greater than that obtained with serial determinations using thromboplastin from the same vial (1.3 per cent for both Simplastin and Acuplastin).

Analysis of the effect of different diluents on dilution curves confirms the observations of others [*2,7*], that the configuration of the curve at greater dilutions is strongly influenced by the nature of the diluent. (Fig. 2.) The curves obtained with 0.85 per cent saline solution and with imidazole saline buffer are in fairly close agreement, but those obtained with barium sulfate-adsorbed plasma are significantly displaced to the left, so that a lower per cent activity value would be assigned to a given plasma clotting time. This would mean that a patient kept at a certain per cent of normal prothrombin complex activity, employing a plasma dilution curve, would have a higher level of plasma clotting factors and a faster plasma clotting time than one kept at the same per cent level, employing a saline dilution curve.

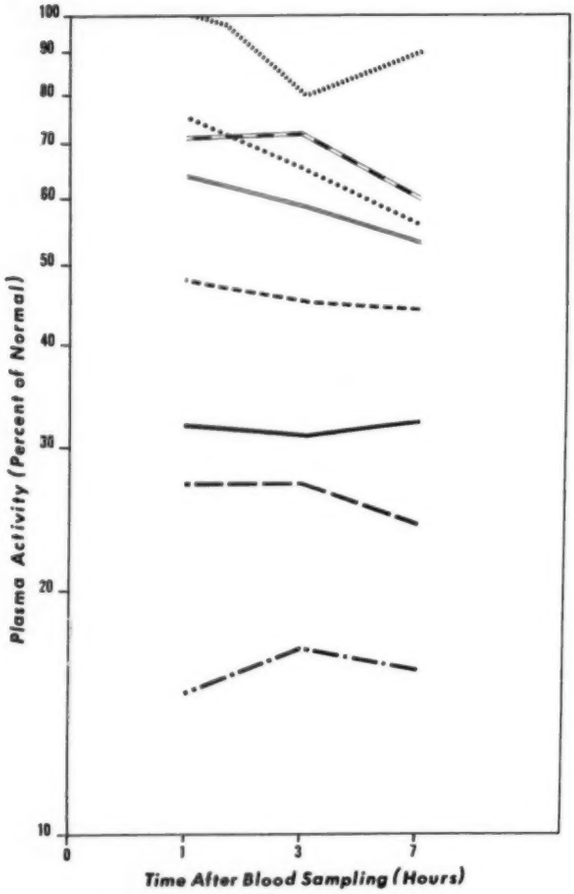

FIG. 3. Relatively small changes resulting from storage of plasma before determination of plasma activity.

TABLE II

VARIATIONS IN PROTHROMBIN COMPLEX ACTIVITY REPORTED BY FOURTEEN HOSPITAL LABORATORIES

Plasma Sample	Highest Value Reported (H) (%)	Lowest Value (Reported (L) (%)	Ratio (H/L)
1	41	12	3.4
2	43	12	3.6
3	42	11	3.8
4	39	12	3.3
5	46	15	3.1
6	35	12	2.9
7	48	18	2.7
8	42	15	2.3
9	27	12	2.3
10	48	17	2.8
Average	...	...	3.1

TABLE III

VARIATIONS IN PROTHROMBIN COMPLEX ACTIVITY REPORTED BY SEVEN HOSPITAL LABORATORIES USING THE SAME THROMBOPLASTIN (SIMPLASTIN)

Plasma Sample	Highest Value Reported (H) (%)	Lowest Value Reported (L) (%)	Ratio (H/L)
1	39	16	2.5
2	42	19	2.2
3	25	16	1.6
4	38	17	2.2
5	45	20	2.3
6	30	13	2.3
7	48	20	2.4
8	44	18	2.4
9	25	12	2.1
10	48	22	2.2
Average	...	...	2.2

The use of refrigerated and non-refrigerated centrifuges resulted in no significant differences in the plasma activity of samples obtained from the same patient at the same time. Storage of plasma at room temperature or in the refrigerator for varying periods up to twenty-four hours produced relatively small changes in prothrombin complex activity. (Fig. 3.) Plasma samples with normal or near normal activity tended to show a fall in activity while plasma from patients whose level was depressed by anticoagulants showed either a slight rise or fall.

The most significant variations in plasma

TABLE IV

COMPARISON OF TWO LABORATORIES USING SIMPLASTIN TO ILLUSTRATE IMPORTANCE OF ACCURATE DILUTION CURVES

Plasma Sample	Laboratory 1		Laboratory 2	
	Seconds	Per cent Activity	Seconds	Per cent Activity
1	24	39	25	18
2	23	42	24	19
3	27	30	28	16
4	24	39	26	17
5	22	45	23	20
6	25	35	31	13
7	21	48	23	20
8	23	42	25	18
9	29	25	33	12
10	21	48	26	17

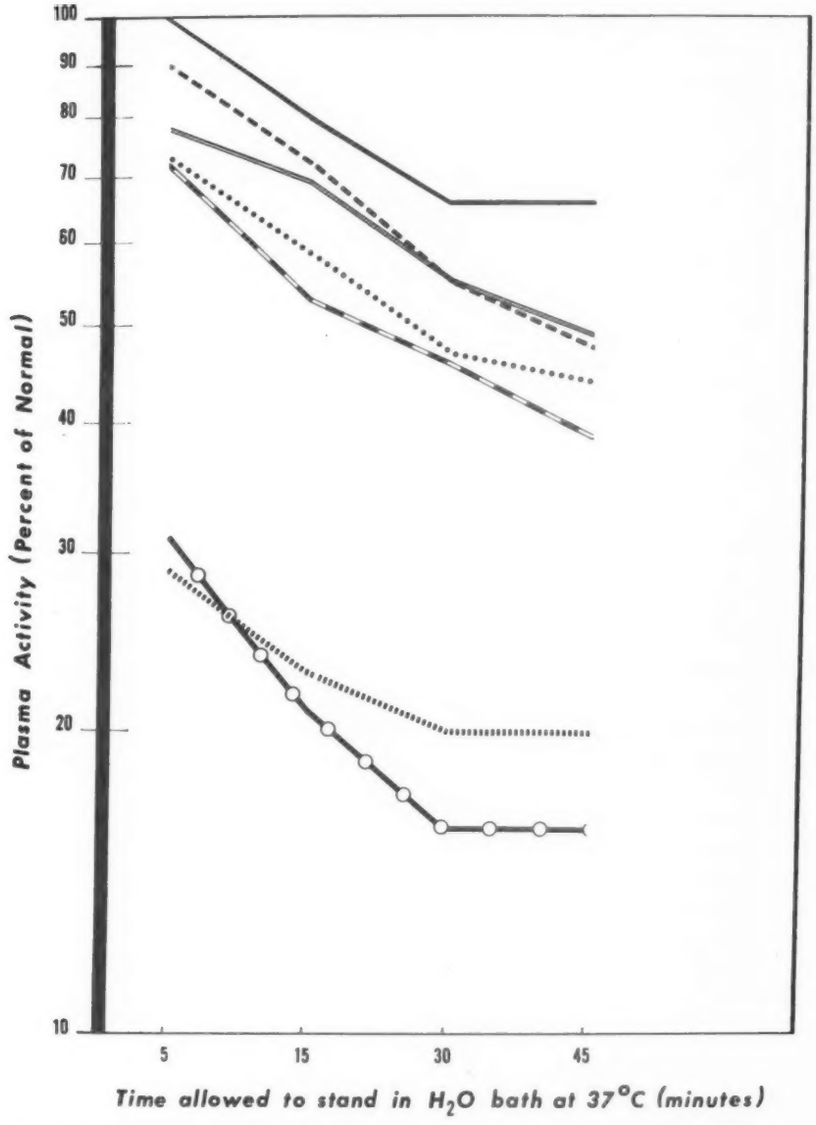

FIG. 4. Marked fall in prothrombin complex activity after prolonged exposure to water bath at 37°C.

activity resulting from alterations in technic were found when samples were permitted to stand in the water bath at 37°C. for five to forty-five minutes. With prolonged exposure to this temperature a uniform decrease in measured prothrombin complex activity was observed. (Fig. 4.) This fall in activity over a period of forty-five minutes varied from 41 per cent in a plasma with an initial value of 90 per cent, to a fall of 9 per cent in a plasma with an initial value of 29 per cent. In each case the decrease was between 30 and 50 per cent of the initial prothrombin complex activity, with an average of 40 per cent.

The results of prothrombin complex activity determinations on the same plasma samples by fourteen hospital laboratories showed a wide range of values for each specimen. (Fig. 5.) The ratio between the highest and lowest values reported for each plasma ranged from 2.3 to 3.8 with an average of 3.1. (Table II.) The results submitted by the seven laboratories using the same thromboplastin preparation (Simplastin) showed a little less variation (Fig. 6) but the highest plasma activity reported for each sample was still from 1.6 to 2.5 times as great as the lowest, with an average ratio of 2.2 between the highest and lowest value. (Table III.) Despite this

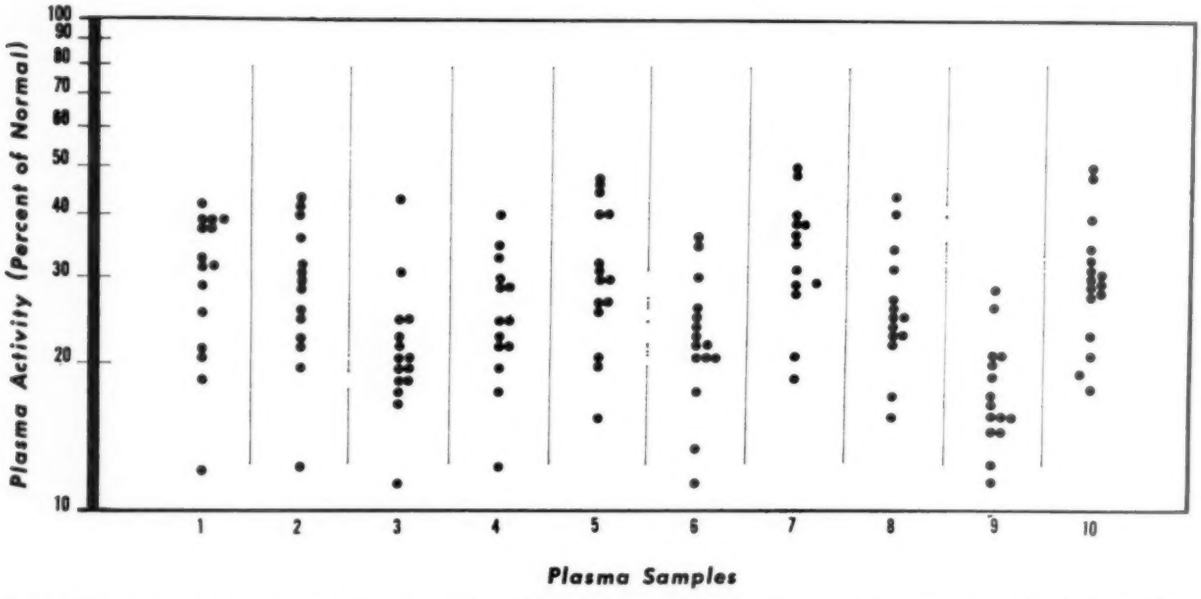

FIG. 5. Wide variation in reported plasma prothrombin complex activity by fourteen laboratories on identical samples.

wide variation in the plasma activity reported as per cent of normal for the same plasma samples by different laboratories, the actual plasma clotting time in seconds showed fairly close agreement in most cases (Table IV), indicating that the error was in the conversion to per cent activity by the use of a dilution curve.

COMMENTS

An evaluation of the influence of variations in technic on the Quick one-stage determination in our laboratory indicates that differences in thromboplastin preparation and differences in the method for preparing dilution curves profoundly affect the results of determination of the prothrombin complex. Except for prolonged exposure to a temperature of 37°C. in the water bath, however, variations in the handling of plasma samples have little influence on results.

It is apparent that there are clinically significant differences among thromboplastin preparations, probably because they measure different

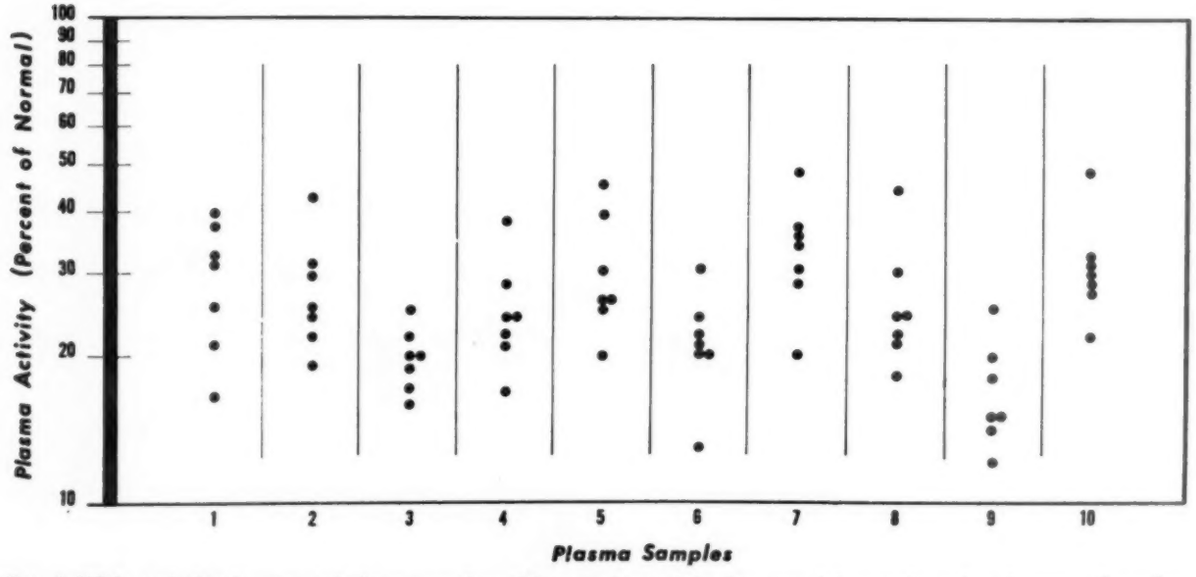

FIG. 6. Wide variation in reported plasma prothrombin complex activity by seven laboratories using the same thromboplastin (Simplastin) on identical samples.

components of the second stage of the clotting mechanism [*2,8*]. This is supported by the observation that the highest plasma activity values were obtained with a brain extract, which apparently has a high factor VII (proconvertin)-like activity, and the lowest with a lung extract, probably low in factor VII-like activity and therefore sensitive to decreases in factor VII in the tested plasma. One would expect, therefore, that the results of two laboratories using different thromboplastins would not be comparable. Although variations in the same brand of thromboplastin were negligible for the two preparations tested, this might become a significant factor if the standardization of a given thromboplastin were poor.

Since the configuration of the dilution curves obtained with different diluents is significantly altered at higher dilutions, the preparation of these curves obviously is a potential source of error. The use of barium sulfate-adsorbed plasma has been advocated because it is free of factor II (prothrombin) and factor VII (proconvertin) but contains other factors which function in the second and third stage of the clotting mechanism. The use of such a diluent results in plasma clotting times at higher dilutions considerably shorter than those obtained with saline solution or imidazole buffer. Reference to such a barium sulfate-adsorbed plasma curve will, therefore, indicate a lower plasma activity for a given plasma clotting time, a range of 5 to 10 per cent on this curve corresponding to the usually accepted therapeutic range of 10 to 30 per cent on a saline dilution curve. Two other sources of error are introduced by the barium sulfate-adsorbed plasma. The reagent is not entirely free of prothrombin and proconvertin, and its content of these factors varies from lot to lot. It also appears to contain some clot accelerating factor, since the plasma clotting times decrease rather than increase at ranges of 60 to 80 per cent. (Fig. 2.)

When the determinations of prothrombin complex activity in the same plasma sample by different laboratories were compared, the differences were even more striking than had been anticipated, the highest values being approximately three times as great as the lowest for each plasma sample. Even when differences in thromboplastin preparation were excluded by considering only the laboratories using one brand (Simplastin) the differences were great, the high values being about twice the low values.

An analysis of the data submitted by the fourteen cooperating hospitals indicates that the chief factor responsible for the differences was the use of incorrect dilution curves for expressing prothrombin complex activity as per cent of normal plasma activity. This is illustrated by the fairly close agreement of the plasma clotting time in seconds obtained by two of the laboratories and the wide difference in the per cent activity they reported. (Table I.) The discrepancy is attributable to the dilution curve used by Laboratory 1, which is displaced to the right of the curve obtained under carefully controlled conditions in our laboratory, and that of Laboratory 2 which is similarly displaced to the left. (Fig. 7.) Reference to the correct curve or to a standard curve provided by the manufacturer would result in close agreement in the results reported by both laboratories.

If the use of dilution curves to express the plasma clotting time in terms of per cent of normal is a potential source of error, one might reasonably ask why they are used at all. The concept was introduced to provide a basis for comparison of results obtained in laboratories using different thromboplastins or in the same laboratory with different batches of thromboplastin. So widespread is the use of per cent values that many laboratories (including five of the fourteen who cooperated in the study) do not normally report the plasma clotting time in seconds at all. Since our results indicate that significantly different values are obtained with different thromboplastins by the same technician, using identical technics, on a single plasma sample, it seems apparent that the basis for using the per cent activity is not tenable. Laboratories using different thromboplastins are actually measuring different factors in the clotting mechanism with the Quick test and their results cannot be made comparable in this way. In practice, a therapeutic range of 15 to 30 per cent in our laboratory might correspond to 30 to 45 per cent in a laboratory using a different thromboplastin, or of 5 to 10 per cent in another laboratory using a third thromboplastin.

In addition to the fact that use of the per cent of normal activity as a basis for comparison between different laboratories is invalid, the dilution curves from which these per cent values are estimated introduce into the determination a source of error that exceeds in importance any of the common technical errors in performance of the test. Some of the difficulty stems

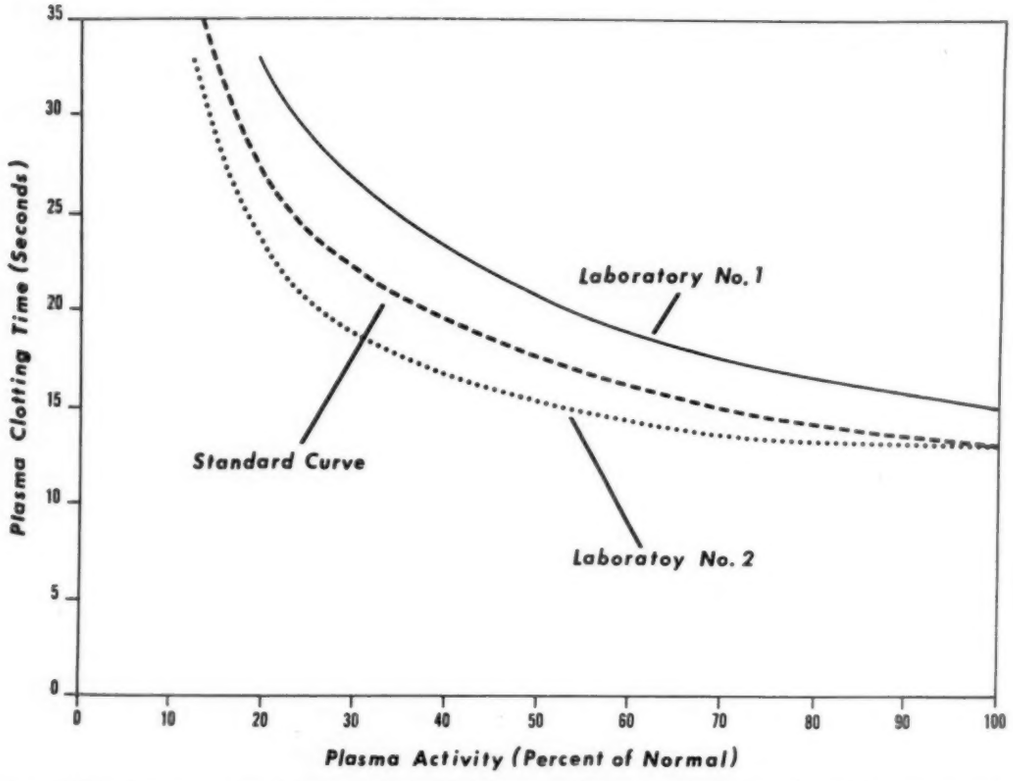

FIG. 7. Dilution curves used by two clinical laboratories for conversion of prothrombin time to per cent of normal activity compared with corrected curve.

from a lack of understanding of the nature and importance of the dilution curve, but it is made worse by the lack of agreement regarding the diluent that should be used, since the diluent greatly influences the configuration of the curve.

The use of different thromboplastin preparations is undoubtedly a second important factor, since results obtained by the same careful technic, using accurate dilution curves in the same laboratory, vary with the thromboplastin employed in the test. The questionnaires also indicated that little emphasis was placed in most of the fourteen laboratories upon the important factor of the duration of exposure to increased temperatures in the water bath. This was not kept constant either in the same laboratory or among the several laboratories.

Ideally, all laboratories should use the same well standardized thromboplastin preparation and should employ comparable technics. This would require some form of central control with cross checks among laboratories, and it is rather unlikely that this can be accomplished on a wide scale. It is quite possible, however, to achieve satisfactory control of anticoagulant therapy by the Quick one-stage test if attention is paid to a few important considerations. The physician should know what thromboplastin the laboratory is using and its relative sensitivity to the factors depressed by anticoagulants of the coumarin type. If possible, serial tests on the same patient should be performed in the same laboratory. The laboratory should report the "control," or clotting time of normal plasma, in addition to the clotting time of the patient's plasma in seconds. It has been our experience that a "control" based on pooled normal plasma gives more consistent and reproducible results than commercial plasma standards. "Standard plasmas" should be used only to check technic for errors. Finally, the errors introduced by dilution curves may be eliminated if physicians accustom themselves to the significance of the plasma clotting time in seconds. For five of six thromboplastins used in the present study, there was a consistent relationship between dilution values and per cent prothrombin complex activity. This relationship was such that one and a half times the normal or control clotting time corresponded to a range of 32 to 38 per cent activity, twice normal clotting

time to a range of 17 to 22 per cent and two and a half times normal to a range of 12 to 14 per cent. This means that a patient whose prothrombin time is maintained at about twice the control values for the laboratory and thromboplastin under consideration will be in the usually accepted therapeutic range, with one and a half and two and a half times the control value as the upper and lower limits.

SUMMARY

An evaluation of the Quick one-stage determination of prothrombin complex activity was undertaken to determine why it has not been entirely satisfactory in clinical practice, and whether its deficiencies can be corrected.

Our results indicate that the test is relatively simple, accurate and, except for prolonged exposure of plasma and reagents to water bath temperatures, not seriously affected by common variations in technic.

The chief source of error in clinical laboratories appears to be the use of incorrect dilution curves for conversion of plasma clotting time to per cent of normal plasma activity. This difficulty is compounded by the controversy regarding the proper choice of a diluent in making these curves.

Until laboratory personnel agree to use the same highly standardized thromboplastin preparation for the test and the same diluent in constructing dilution curves, conversion to per cent of normal plasma activity will not provide a satisfactory basis for comparison of results from different laboratories, and the results are better expressed in seconds.

With attention to standardization of technic the one-stage determination of prothrombin, complex activity is a satisfactory method for the control of anticoagulant therapy with coumarin-like agents.

Acknowledgment: We wish to express our appreciation for the technical assistance of Mrs. Esther H. Wolfe.

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Fibrinolysis Induced by Pressor Amines*

EDWARD GENTON, M.D., FRED KERN, JR., M.D. *and* KURT VON KAULLA, M.D.
Denver, Colorado

FIBRINOLYSIS has important implications for clinical medicine. Excessive fibrinolytic activity can be a factor in dangerous hemorrhage; this is occasionally encountered during shock, following major surgery and in other conditions [*1–3*]. On the other hand, the controlled infusion of fibrinolytic enzymes or fibrinolysis-inducing enzymes has recently been employed to dissolve intravascular clots in the treatment of thromboembolic disorders [*4–16*].

The biochemical and physiologic control of the fibrinolytic system is only partially understood. Despite its complexity, sensitive and reliable technics for measurement of fibrinolytic activity have been developed [*18*]. Recently it has been demonstrated that a variety of drugs activate the fibrinolytic system in man [*18,19,21, 31,32,34*]. The implications of drug activation of the system are threefold: (1) the drugs might serve to provide more insight into the mechanism of the fibrinolytic system, (2) a pharmacologically-induced fibrinolysis becomes more feasible, (3) the possibility of drug-induced fibrinolytic hemorrhage has to be considered under certain conditions.

Epinephrine has been shown to activate the system [*19–21*], but neither the effect of intravenously administered epinephrine nor that of other pressor amines has been thoroughly investigated. The purpose of this study was to characterize the effect of epinephrine and other commonly used pressor amines on fibrinolytic activity in normal man.

In the interest of clarity, the mechanism of fibrinolysis as it is presently understood will first be discussed briefly. Figure 1 represents the scheme generally accepted for the steps involved. All components of the system are proteins.

The basic process is the destruction of a fibrin clot by the enzyme, plasmin. Plasminogen, the inactive precursor of plasmin, is probably synthesized in the liver [*22*]. It can be converted

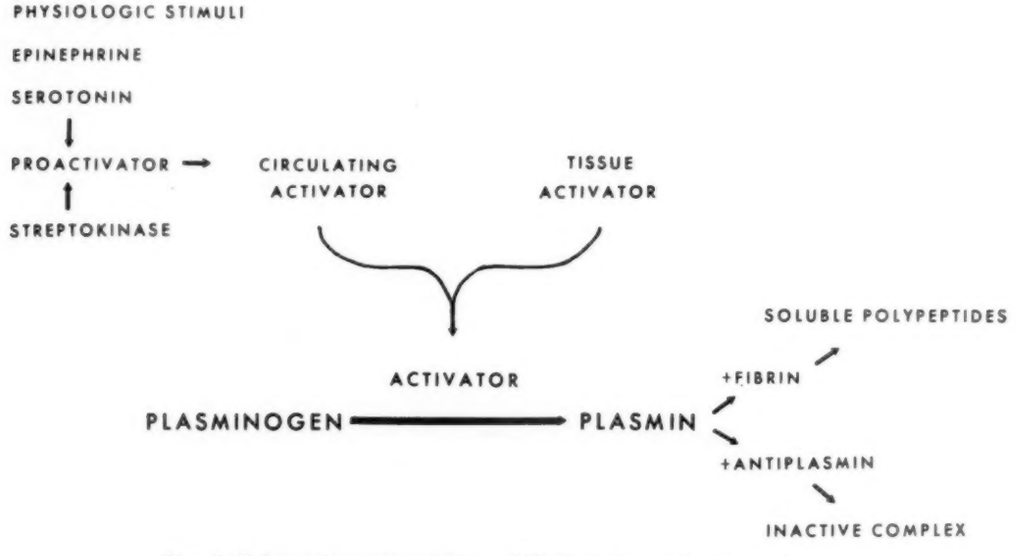

FIG. 1. Schematic representation of fibrinolytic mechanisms of man.

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to plasmin either in the plasma or within the interstices of a clot, where it is selectively adsorbed by fibrin strands [*20,22,23*]. Small amounts of plasmin are probably always present in the circulation, but are inactive due to the binding powers of antiplasmin [*20*]. When, however, plasmin is formed within a clot, where the effective antiplasmin activity is low, it splits specific linkages holding fibrin monomers together [*25*], resulting in lysis.

The albumin fraction of plasma contains antiplasmin [*26*] in an amount in excess of that required to inhibit the plasmin produced by the activation of all circulating plasminogen [*17*].

The conversion of plasminogen to plasmin is catalyzed by one of several activators which split off a peptide group from plasminogen [*17*]. The size of this peptide group may vary with different activators and the resultant plasmin may possess different properties [*24*]. For example, the fibrinolytic enzyme found after exercise, epinephrine injection or sudden death affects fibrin but does not digest fibrinogen, casein or gelatin, whereas plasmin formed by streptokinase activation affects all these substances [*17,24,27*].

In man there are apparently two types of substances that activate the conversion of plasminogen to plasmin. Further work may reveal them to be derivatives of the same substance. One of these escapes from tissue under abnormal circumstances which injure or cause the death of cells. This material, an intracellular protein, is acid- and heat-stable and capable of degrading plasminogen directly [*24*]. It is present in high concentrations in the uterus, adrenals, lymph nodes, prostate and thyroid; the heart, brain and skeletal muscles are nearly devoid of it [*22,26*]. The other activator, a heat- and acid-labile substance, is responsible for activation of the system under physiologic circumstances, such as stress and exercise [*1,19,28*]. The source of this material is not entirely clear. It possibly is produced when its precursor, proactivator, is acted upon by a factor released from the endothelial lining of capillaries and veins during stress and exercise, and after other stimuli [*23, 29,30*]. Appreciation of this concept is important because the alteration in lytic activity observed in man is probably due to changes in the amount of circulating activator [*31,32*], and not to decrease in inhibitors as has been suggested [*33*].

The role of epinephrine in activation of the human fibrinolytic system is not clear. It has no effect *in vitro* ([*20*] present study) and the fibrinolytic effect produced is not related to the presence or absence of formed elements of the blood, adrenals, spleen, liver, pancreas or bone marrow [*20*]. It is presumed that epinephrine causes the release of activators possibly from the walls of capillaries or veins [*23,32*]. Studies to date have used the subcutaneous [*19,21*] or "paravenous" [*30*] routes of administration and produced shortened lysis time for ten to thirty minutes. In one study 1 μg. of epinephrine and 2 to 4 μg. of norepinephrine were given intravenously in man without effect [*21,30*].

MATERIAL AND METHODS

Twelve "normal" patients were studied. They were selected from the wards of the Colorado General Hospital and the Denver Veterans Administration Hospital. They were not ill at the time of study.

Each patient was studied at rest after an overnight fast. An 18 gauge needle was inserted into an antecubital vein and kept open throughout the procedure by small amounts of 2.5 per cent sodium citrate solution [*34*]. After three control observations at fifteen-minute intervals over a period of forty-five minutes a pressor amine was given intravenously and samples were drawn from a needle kept in the other arm without cuffs or tourniquets [*29,30*]. Samples were taken at frequent intervals beginning two minutes after the injection and continuing forty-five to sixty minutes. The assay for lytic activity was begun immediately and incubation of the euglobulin clot was started within thirty minutes.

The drugs used were epinephrine, norepinephrine and phenylephrine. Two types of studies were made: (1) The drug was injected during a five-minute period and in several experiments multiple such injections were given at hourly intervals, and (2) the drug was infused at a constant rate for one hour. The blood pressure and pulse rate were monitored carefully during the infusions and subjective symptoms observed.

A slightly modified euglobulin lysis method was used to measure lytic activity [*18*]. This consists of collecting 4 ml. of blood in a syringe containing 1 ml. of 3.8 per cent sodium citrate solution [*34*], using the double syringe method to avoid contamination with tissue substances. The blood was centrifuged at once at 1,000 × g at 0°C. for four minutes. One milliliter of plasma was then diluted with 15 ml. of water in a 50 ml. Erlenmeyer flask to separate the plasmin-antiplasmin complex [*17,34*]. The euglobulin fraction was precipitated by passing a stream of carbon dioxide over the solution for four minutes, with constant mixing by means of a magnetic stirrer. This lowers the pH to approximately 5.6 and precipitates the euglobulin fraction while permitting the albumin fraction

TABLE I
EFFECT OF PRESSOR AMINE INFUSION (FIVE MINUTES) ON EUGLOBULIN TIME

Case No.	Age (yr.) and Sex	Diagnosis	Euglobulin Lysis Time (min.)		Decrease	
			"0" Time	Minimum	Absolute (min.)	Per cent
		Epinephrine				
I	44,M	Ulcer	132	35	97	73
II	47,F	Ulcer	72	37	35	49
III	46,M	Ulcer	203	40	163	80
IV	39,M	Ulcer	89	32	57	64
V	31,M	Ulcer	187	48	139	74
VI	15,M	Pneumonia	135	85	50	37
VII	40,M	Gastritis	185	54	131	71
VIII	29,M	Pneumonia	185	45	140	76
		Phenylephrine				
III	46,M	Ulcer	165	88	77	47
IV	39,M	Ulcer	92	52	40	43
V	31,M	Ulcer	233	125	108	46
VI	15,M	Ulcer	196	79	117	59
VII	40,M	Gastritis	167	49	118	71
		Norepinephrine				
IV	39,M	Ulcer	151	85	66	44
V	31,M	Ulcer	187	95	92	49
VIII	29,M	Pneumonia	162	92	70	43

containing antiplasmin to remain in solution. The euglobulin fraction contains all components of the fibrinolytic system except antiplasmin, together with about 25 per cent of the circulating fibrinogen and other clotting factors [*33*]. After centrifugation at room temperature at 1,000 × g for three minutes, the supernatant was discarded and the inner wall of the centrifuge tube wiped dry to remove any antiplasmin remaining. The precipitate was then redissolved by adding 1 ml. of a saline barbital buffer, pH 7.42; 0.3 ml. of this solution was transferred to a 10 by 75 mm. tube and immediately clotted with 0.01 ml. of a human thrombin solution made by dissolving 1,000 units of thrombin (Parke-Davis) in 5 ml. of 50 per cent glycerin. The tube was then incubated in a glass water bath at 37.5°C. The end point was reached when complete dissolution of the clot occurred. Duplicate determinations were made with the unaltered plasma. The normal lysis time by this method was between 120 and 300 minutes, with less than 10 per cent variation in duplicate. This is similar to the normal range described by others [*18*].

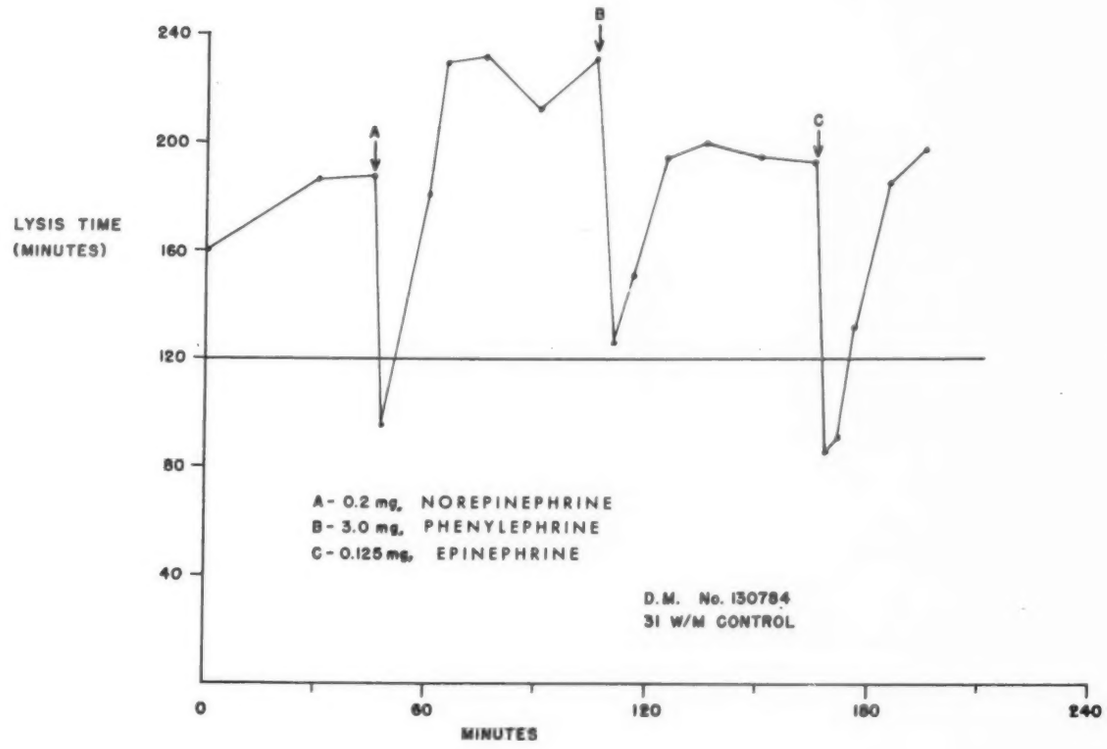
In several patients the euglobulin lysis time was compared with the clot lysis time obtained by the whole plasma clot technic in which unaltered plasma is clotted by the addition of 0.1 ml. of thrombin solution and incubated until clot lysis occurs [*35*].

RESULTS

There was considerable variation in the subjective response to the administration of pressor agents in normotensive subjects. The symptoms most often encountered were nervousness, mild anxiety, "tightness" in the chest (not thought to be angina), breathlessness, palpitation, low lumbar back pain and throbbing headache, usually occipital. The latter was not directly related to blood pressure, and was especially severe following injection of even very small doses of norepinephrine. It reached excruciating proportions in several patients and accounts for the small number of subjects given norepinephrine.

The hypertension produced by all drugs was quite variable but in most subjects the systolic blood pressure reached 200 to 220 mm. Hg; if it went higher the infusion was slowed. Slight bradycardia usually occurred and no instance of tachycardia was noted. There was no correlation between either the subjective symptoms or degree of hypertension and the extent of decrease in lysis time. Patients perfused for an hour usually noted decrease in subjective symptoms after five to ten minutes. The blood pressure stabilized around 180 to 200 mm. Hg and the pulse between 60 and 80.

In no subject did the euglobulin lysis time fall below 120 minutes during the forty-five-minute control period. All patients responded to the intravenous administration of the three drugs by a shortened euglobulin lysis time. (Table I.) The lysis time decreased from 37 to 80 per cent below the levels existing before injection. Figure 2A shows the response in a patient given each of the drugs at hourly intervals. All substances shortened lysis time to about the same degree, but none of them produced very low values. Figure 2B demonstrates an experiment in which the lysis time fell to less than forty minutes. The maximum fall in lysis time was usually two minutes after the infusion was terminated. Samples drawn during the time of injection (in other patients) indicated only a slight response, until about one minute after the injection. After one or two minutes of shortened



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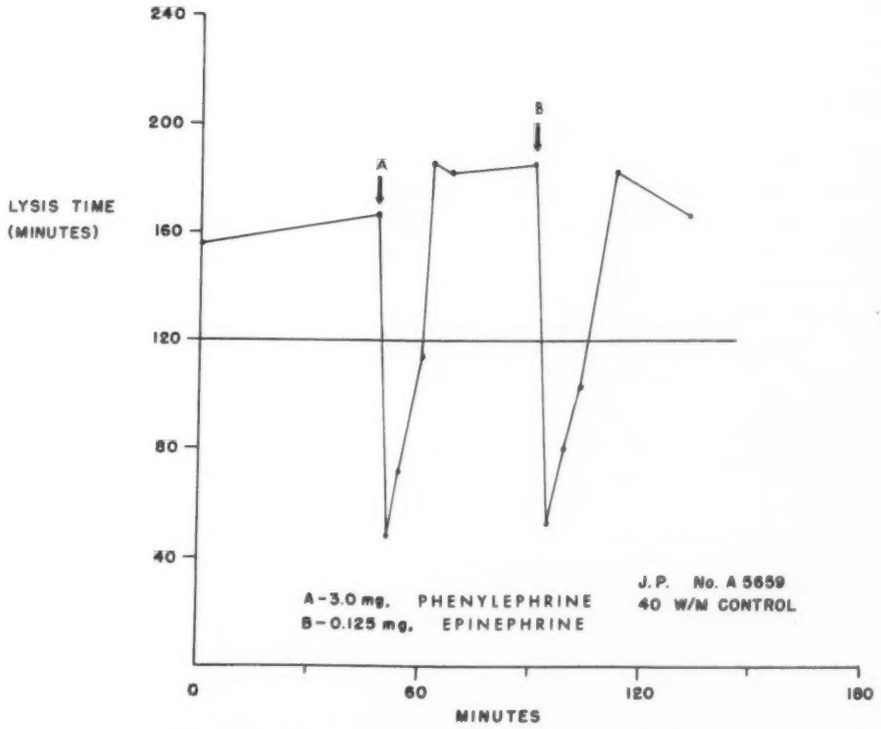

2B

FIG. 2. A, the response to the serial administration of various pressor amines on euglobulin lysis in a thirty-one year old man. The pressor effects of the drugs were equivalent. B, a marked fall in euglobulin lysis time occurred in response to the administration of both phenylephrine and epinephrine.

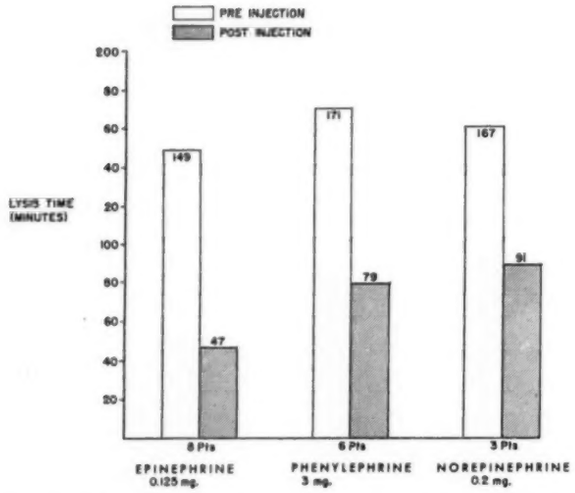

FIG. 3. Mean fibrinolytic response of euglobulin lysis in normal subjects to pressor amines.

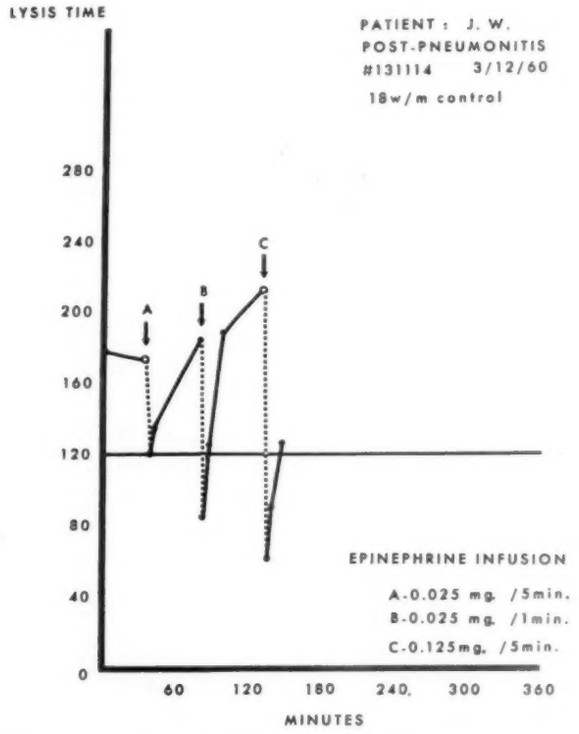

FIG. 4. Dose-time relationship of epinephrine-induced fibrinolysis.

lysis time there was a prompt return toward normal. This was expected because the half-life of injected epinephrine is one to two minutes and that of norepinephrine four to eight minutes [*36*].

The apparent "overshoot" to a value above the control time following stimulation has been described previously and is said to last several hours [*35*]. This was observed several times, but not consistently, and did not prevent response to repeated drug administration within twenty minutes.

Comparison of Pressor Drugs. Figure 3 indicates the mean responses to the various drugs. Epinephrine produced the greatest response but in some subjects the maximum fall in lysis time occurred after either of the other pressor drugs. The magnitude of response was not affected by the sequence of administration. Although the doses used produced equivalent effects, the mean fall in euglobulin lysis time was 66 per cent after the administration of epinephrine, 53 per cent after phenylephrine and 44 per cent after norepinephrine.

Effect of Dose Variation. To determine the importance of the total dose administered and the duration of the infusion the following experiment was carried out. (Fig. 4.) After the usual control period, 0.025 mg. of epinephrine (one fifth the usual 0.125 mg. dose) was given during five minutes. This caused the lysis time to decrease only 31 per cent. After it returned to normal the same amount was given during a one-minute period, thus reproducing the usual rate of administration, and the lysis time then decreased 54 per cent. Finally, the patient received the usual 0.125 mg. over five minutes, with a 72 per cent fall in lysis time. In other subjects the injection of twice the usual dose of epinephrine during two or three minutes caused less shortening of the lysis time than the usual 0.125 mg. injection given over five minutes. It therefore appears that both the total amount administered and the rate of administration are important in determining the effect on fibrinolysis.

Comparison of Technics (Euglobulin Lysis Time Versus Plasma Lysis Time). In several experiments fibrinolysis was measured by the euglobulin lysis technic and by the plasma clot technic on the same samples of blood. In each instance the changes in lysis time determined by the two methods were concordant. The absolute values obtained by these technics were not closely related, but some general conclusions are possible. A euglobulin lysis time of forty minutes or less was accompanied by a plasma lysis time of one to four hours; a fifty-minute euglobulin lysis time was accompanied by a plasma lysis time of around six hours, and the lower normal euglobulin lysis time of 120 minutes was usually associated with a plasma lysis time of around

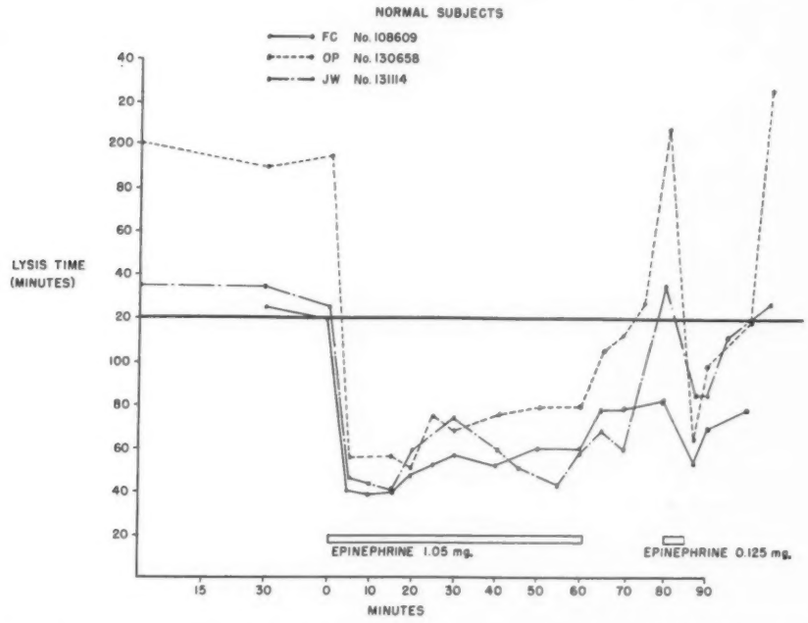

FIG. 5. An infusion of epinephrine for one hour produced sustained shortening of the euglobulin lysis time in each of three subjects. Twenty minutes after the infusion an injection of epinephrine was again followed by shortening of the lysis time.

twenty-four hours. Euglobulin lysis times longer than 120 minutes were occasionally obtained with plasma lysis times of forty-eight hours or longer. These findings do not substantiate other reports which describe no correlation between euglobulin and whole plasma lysis times (using diluted plasma) [*33*].

Effect of Repeated Administration. Previous reports have claimed that activation of the lytic system by the injection of pyrogen is followed by a refractory period which lasts several hours and which may be overcome by larger doses [*35*]. Our studies, however, showed no alteration in response to different drugs given at hourly intervals. (Fig. 2.) Moreover, in two normal subjects and one patient with cirrhosis of the liver the same drug was administered at hourly intervals for three to five hours, and in each patient the lytic system was activated to the same extent after each injection; there was no evidence of a refractory period or that "depletion" of the system occurred or that tolerance developed.

Effect of Prolonged Infusions of Vasopressor Drugs on Fibrinolytic Activity. Figure 5 illustrates the results in three normal subjects who received an infusion of 1.05 mg. of epinephrine in one hour. The response was prompt, to low values, and sustained throughout the time of infusion. An escape from the drug is suggested in two patients in whom there was a slight rise in lysis time after the first fifteen or twenty minutes. This may have been due to variation in the rate of administration necessary to lessen symptoms. In other patients (with hepatic disease) we have demonstrated that speeding the rate of administration toward the end of the infusion period resulted in an even further decrease in lysis time. There was a prompt return to control lysis time in two of the three subjects included in Figure 5. Twenty minutes after the infusion was terminated each patient received the usual dose of epinephrine (0.125 mg.) as a five-minute infusion. The magnitude of response to that injection was similar to that produced by the infusion. Thus even after maintaining increased fibrinolytic activity for an hour there was no evidence of refractoriness or depletion of the lytic system.

COMMENTS

The euglobulin lysis method for measuring fibrinolytic activity has been reported to be sensitive and reliable [*18,31,33*]. It is primarily considered to be a measure of activator concentration [*31*]. Since the activator is thought to represent the most important variable in the system [*32*], a method of measuring its increase after stimulation of fibrinolytic system is very

useful. The studies reported herein confirm the sensitivity, reproducibility and usefulness of the method. They do not, however, answer the criticism that the method is not sensitive enough to differentiate between very short lysis times [*31*]. It has been reported that when the euglobulin lysis time falls to fifty minutes or less a bleeding tendency may be aggravated; and when it falls to seven minutes or less, bleeding from fibrinolytic activity is impending [*18*].

The significant correlation between euglobulin lysis and plasma lysis suggests that the plasma clot method might well be useful for evaluating lytic activity in sick patients. If the plasma lysis time exceeds eight to ten hours, significant lytic activity would be unlikely although such values may be dangerous after surgery. More important, however, is the observation of a parallel fall in lysis time with the two technics following activation with pressor amines. This suggests that these drugs effect a true alteration in the fibrinolytic system. It is measurable in unaltered plasma (containing all components of the system including inhibitors) as well as in a system in which certain components have been removed in order to provide a faster and more sensitive measure.

Our studies show that the activating effect on fibrinolysis produced by epinephrine is not peculiar to this pressor substance. A similar response was observed following the administration of both phenylephrine and norepinephrine, but in most subjects the effect was slightly less pronounced than after the administration of epinephrine. While the mechanism by which this activation is produced is not entirely clear, it occurs promptly, is marked in degree, can be recalled almost immediately without increasing the dose, and can be maintained by constant infusion for one hour. The effect seems related to both the dose and the time used for its injection; activation of fibrinolysis is slight even after a large dose if it is given in less than five minutes. There is no correlation between the pressor response or subjective symptoms and the degree of fibrinolytic activation produced.

These observations have two practical clinical implications: (1) In patients who receive pressor amines by continuous infusion significant and sustained fibrinolytic activity could develop. It is easy to imagine situations, such as hemorrhagic or postoperative shock, in which such activity would be potentially harmful. If further study confirms our preliminary finding that norepinephrine is less likely to produce marked activity than the other pressor drugs, this consideration would be important in selecting the proper drug for continuous infusion in hypotensive patients. When excessive bleeding occurs in patients receiving intravenous pressor agents, fibrinolysis may be a contributing factor. (2) Since it appears that the fibrinolytic activating effects are not closely related to the hypertensive effects, the therapeutic use of pressor amines is suggested. If a related substance can be found with minimal pressor effect and maximal fibrinolytic effect it might prove valuable in the treatment of thrombotic states. The presently employed thrombolytic agents such as streptokinase or plasmin have numerous disadvantages [*24,27*]. (Activation of thrombolysis by endogenous stimulation by pressor amines seems more physiologic.) Furthermore, it could be maintained for a long period without depletion of protein substances such as fibrinogen and without the development of a resistant state.

SUMMARY

The effect of the pressor amines, epinephrine, norepinephrine and phenylephrine, on fibrinolytic activity was studied in twelve normal subjects. The drugs were given intravenously either by five-minute or one-hour infusion. Fibrinolytic activity was measured by the euglobulin lysis technic, and in some experiments compared with whole plasma clot lysis time.

A significant activation of fibrinolysis was promptly produced by all three drugs. This fibrinolytic activity could be repeatedly recalled or maintained by constant infusion.

Acknowledgment: We are indebted to Mrs. Geraldine Fairchild for her valuable technical assistance.

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Serum Globulin Deficiencies in Non-Tropical Sprue, with Report of Two Cases of Acquired Agammaglobulinemia*

KENNETH A. HUIZENGA, M.D., ERIC E. WOLLAEGER, M.D., PAUL A. GREEN, M.D. *and* BERNARD F. MCKENZIE, M.S.

Rochester, Minnesota

AMONG the published cases of acquired agammaglobulinemia, a sprue-like syndrome has been reported in at least eight [*1–8*]; Gitlin and associates [*9*] estimated the incidence of this syndrome in such cases as about 20 per cent. Such an incidence appears to be far too great to be altogether coincidental. Our study of serum globulins in sprue was stimulated by the observation of two cases in which non-tropical sprue and agammaglobulinemia coexisted. It is our aim to report these two cases and to present evidence, obtained from a review of the records in 124 cases of non-tropical sprue, that deficiencies in serum globulin, with or without associated reductions in serum albumin, occur frequently in this disease. These data and also an increase in the concentration of gamma globulin toward normal in one of our patients during a remission of sprue suggest that malabsorption may be an important causative factor in some cases of acquired agammaglobulinemia.

CASE REPORTS

CASE 1. A fifty year old woman came to the Mayo Clinic in August 1954 with a chief complaint of recurrent pneumonia for the previous sixteen years. The past history revealed an excessive number of infections beginning at the age of two years with pneumonia and otitis media. At age eight she was operated on for a perforated appendix, followed by a long convalescence. Frequent attacks of acute tonsillitis occurred during her "teens." Otitis media was a frequent complication of these infections, and it recurred at ages thirty-one and thirty-two. Numerous episodes of pneumonia occurred subsequent to 1938; she averaged one attack every six to eight weeks. Bronchoscopic examination and bronchograms performed in 1950 had not disclosed any abnormal findings. In October 1953 the patient had experienced diarrhea for two months; this recurred in April 1954 for one month.

General examination was within normal limits. Results of routine hematologic tests and urinalysis were normal. The serum contained 4.04 gm. of albumin and 1.2 gm. of globulin per 100 ml. Electrophoresis of serum proteins by both the Tiselius and paper technics revealed complete absence of gamma globulin. On a specimen of serum containing 4.5 gm. of protein per 100 ml., paper electrophoresis disclosed 3 gm. albumin, 0.29 gm. $alpha_1$ globulin, 0.59 gm. $alpha_2$ globulin, 0.64 gm. beta globulin and no gamma globulin. The feces contained Giardia lamblia. Proctoscopy and roentgenologic examination of the stomach and colon revealed no abnormalities. A special study [*10*] of intravenously injected gamma globulin labeled with radioiodine (I^{131}) revealed a half-life of eleven days with one lot and twenty-four days with a second preparation; both values are within the normal range. A transfusion of plasma containing 13.3 gm. gamma globulin accompanied the second injection of labeled protein. The unlabeled gamma globulin quantitated by the electrophoretic method had a half-life of twenty days [*10*].

The diagnosis of acquired agammaglobulinemia was established, and treatment with the intermittent prophylactic administration of antibiotics as well as regular injections of gamma globulin at three-week intervals was instituted.

At the patient's second admission in June 1957 her complaints were anorexia and loss of 17 pounds during the previous two years and intermittent diarrhea for three years. The infections had been fairly well controlled, and pneumonia had not recurred. During the three weeks prior to examination, she had received 12 ml. of gamma globulin, the last injection being given three days prior to admission. Examination, including proctoscopy, disclosed no abnormalities except for glossitis. During the course of this

* From the Sections of Biochemistry and of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
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admission, acute otitis media developed. The serum electrophoretic pattern revealed a very low gamma globulin, 0.18 gm. per 100 ml. The values for the other fractions were 2.93 gm. albumin, 0.49 gm. $alpha_1$ globulin, 0.71 gm. $alpha_2$ globulin and 0.57 gm. beta globulin. The feces contained 21.4 gm. fat and 1.97 gm. nitrogen per twenty-four hours. The serum carotene level was abnormally low, with a value of 8 International Units. There was 1 per cent absorption of vitamin B_{12} labeled with radiocobalt (Co^{60}), which increased to only 5 per cent after intrinsic factor was added. Roentgenologic studies of the small intestine showed a deficiency pattern, those of the gallbladder and stomach disclosed no abnormalities. The additional diagnosis of non-tropical sprue was established, and the patient was instructed to adhere to a gluten-free diet in addition to the antibiotics and gamma globulin.

The third admission was in October 1958 at which time the patient was asymptomatic. She had not received any gamma globulin since July 1958 because the serum gamma globulin at that time had measured 0.22 gm. Further infections had not occurred. The sprue had subsided, and the patient passed only one formed stool per day. She had gained 25 pounds during the previous year. General examination revealed no abnormalities. Electrophoresis of her serum, which contained 5.6 gm. protein per 100 ml., showed 3.1 gm. albumin, 0.38 gm. $alpha_1$ globulin, 0.76 gm. $alpha_2$ globulin, 1.08 gm. beta globulin and 0.28 gm. gamma globulin. The serum carotene was normal (142 International Units), as were the prothrombin time and the serum calcium, phosphorus and iron. The feces contained 9.5 gm. fat and 2.6 gm. nitrogen per twenty-four hours. Roentgenologic studies of the small intestine disclosed great improvement, with little evidence of a deficiency pattern except for some coarsening of the mucosal folds. Absorption of Co^{60}-vitamin B_{12} still was at a very low range of normal; before intrinsic factor was added to the dose, only 1 per cent of the tagged vitamin B_{12} was excreted in the urine in twenty-four hours; after the addition of intrinsic factor, 8 per cent was excreted.

The patient returned in August 1960 with symptoms and findings of carcinoma of the stomach. Laparotomy revealed an inoperable grade 3 adenocarcinoma of the stomach, and a palliative gastroenterostomy was performed. Biopsy of the upper part of the jejunum near the site of the anastomosis disclosed minimal mucosal changes consistent with non-tropical sprue.

Case II. A twenty-five year old man came to the clinic in 1947 with a fourteen year history of diarrhea. He had been robust as a child until the age of twelve years, at which time he had had an acute attack of nausea, vomiting and diarrhea, with twelve stools daily, and a loss of 20 pounds. Since this initial episode, he had experienced recurrent diarrhea, abdominal distress and distention, with watery and light-colored stools. In 1943 there had been episodes of acute arthritis of the left knee associated with red, swollen and painful joints. In 1946 he had experienced tetany, purpura of the legs and recurrent arthritis involving the right knee; in the same year, he had noted frequent colds and intermittent episodes of fever with temperatures up to 104°F. lasting from seven to ten days.

He weighed 82 pounds. The blood pressure was 105 mm. Hg systolic and 75 mm. Hg diastolic. The skin was melanotic. There was slight abdominal distention, no masses or organs were palpable. Some clubbing of the fingers was present. Proctoscopic examination gave normal results.

The value for hemoglobin was 14.4 gm. per 100 ml. blood. The erythrocytes numbered 4,001,000 per cu. mm. of blood and some macrocytosis was noted. The reticulocyte count was 1.1 per cent, the platelet count was normal. The bleeding, coagulation and clotting times were normal, while the Quick prothrombin time was increased to forty seconds (normal is seventeen to nineteen seconds). After two days of administration of a synthetic, water-miscible preparation having vitamin K activity, the prothrombin time became normal (seventeen seconds). Roentgenologic studies revealed a deficiency pattern of the small intestine. The serum calcium measured 7 mg. per 100 ml., the serum phosphate was 3.4 mg., blood cholesterol 117 mg. per 100 ml., and cholesterol esters 44 mg. per 100 ml. The serum proteins totaled 4.6 gm., with 3.8 gm. albumin and 0.8 gm. globulin. Achlorhydria was present after an Ewald test meal. The presence of steatorrhea was confirmed by quantitative stool examination, fat comprising 56.6 per cent of the dry weight of the feces. The urinary 17-ketosteroids measured 4.4 mg. per twenty-four hours. Results of the thymol turbidity and cephalin-cholesterol flocculation tests were normal. There was impaired absorption of vitamin A. Isohemagglutinins for types A and B erythrocytes were absent. The sternal marrow was hyperplastic, and it did not contain any plasma cells.

A diagnosis of non-tropical sprue was established, and hospital treatment was given in the form of a high-carbohydrate, high-protein, relatively low-fat diet supplemented by folic acid, concentrated liver extract given intramuscularly three times weekly, supplemental vitamins and calcium lactate. In thirty-two days the patient gained 21 pounds, looked and felt better, and passed only three formed stools per day. He was dismissed from the hospital with the advice to continue this regimen. The serum total proteins increased to 6.5 gm. per 100 ml., with 5 gm. albumin and 1.5 gm. globulin.

One year later, at the time of his second admission, for a follow-up examination, the sprue was in remission. He weighed 117 pounds. He was having two bowel movements per day. Hemoglobin was 13.2 gm.,

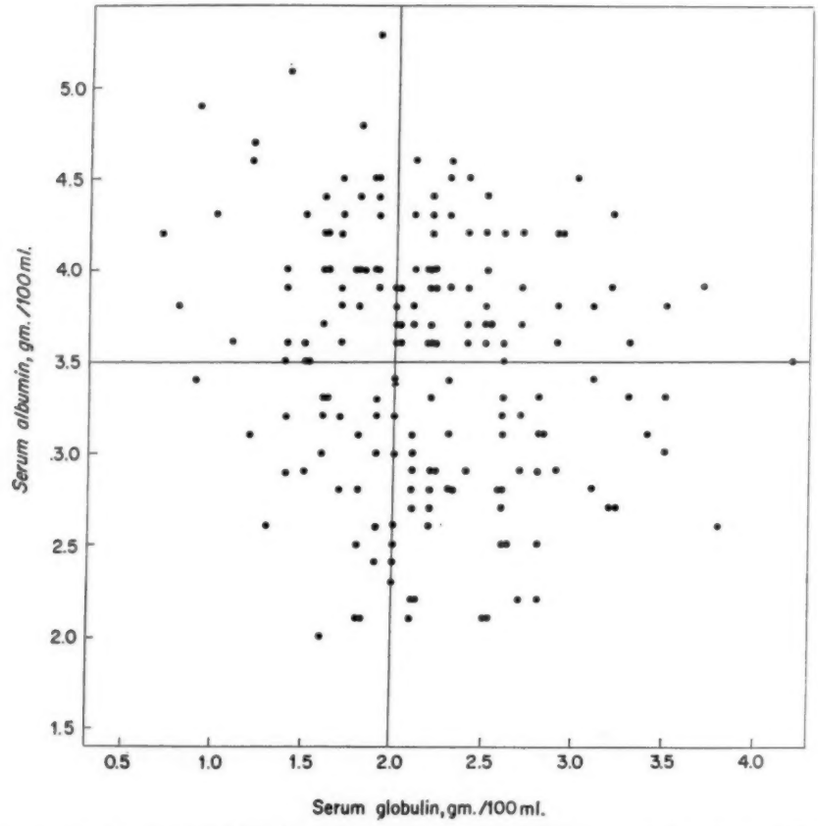

FIG. 1. Scattergram of 178 determinations of serum albumin and globulin in 103 patients with non-tropical sprue. The lower limit of normal is represented by the horizontal and vertical lines.

with erythrocytes numbering 5,001,000 and leukocytes 9,500 per cu. mm. The erythrocytic sedimentation rate was 2 mm. during the first hour (Westergren method). The prothrombin time was slightly increased to twenty-one seconds, and the serum calcium was normal (9.2 mg.). The serum proteins totaled 5.8 gm. per 100 ml., with 4.9 gm. albumin and 0.9 gm. globulin. Isohemagglutinins now were present, with an anti-A_1 titer of 1:16, an anti-A_2 titer of 1:4 and an anti-B titer of 1:4. He was dismissed without changes in his program of treatment.

The third admission (April 1950) was occasioned by a severe relapse that had begun shortly after his dismissal in 1948. It was characterized by progressive loss of weight to 92 pounds, the passage of four to eight loose and watery stools every day associated with abdominal distention and flatulence, and numbness and tingling of the fingers and toes suggesting tetany. Hemoglobin measured 12.4 gm., with erythrocytes numbering 3,630,000 and leukocytes 13,000 per cu. mm. Blood smear showed some anisocytosis with macrocytes and some hypochromasia. The prothrombin time was twenty-one seconds. The serum proteins totaled 5.1 gm., with 4.4 gm. albumin and 0.7 gm. globulin. The serum calcium was 4.8 mg., the phosphate was 2 mg. per 100 ml. Isohemagglutinins were absent. Roentgenologic studies showed an extremely severe deficiency pattern involving the entire small intestine. A seventy-two-hour stool collection revealed 21.1 gm. fat per twenty-four hours while the patient was ingesting a low-fat diet (less than 75 gm. per day).

Hospital treatment was instituted for twenty-six days, with a program similar to that employed during the first admission; in addition, 12 units of human serum albumin were administered intravenously. The symptoms of sprue were relieved only partially at the time of dismissal.

The patient was admitted for the fourth time in June 1950 in a severe relapse, with six to twelve loose stools every day. Anorexia was severe and his weight had decreased to 87 pounds. The hemoglobin was 11.8 gm., and erythrocytes numbered 5,001,000 per cu. mm. The following values in milliequivalents per liter were noted: plasma chlorides, 91.3; plasma carbon dioxide-combining power, 20; serum sodium, 140; serum potassium, 2.4. The serum proteins totaled 5.1 gm., with 3.6 gm. albumin and 1.5 gm. globulin. The serum calcium was 4.6 mg., and the serum phosphate was 1.2 mg. per 100 ml.

Hospital treatment was instituted and continued for sixty-five days. In addition to the measures previously employed, he was given succinylsulfathiazole on two separate occasions, large amounts of vitamin B_{12} (50 μg. every second day), pancreatin and serum albumin. At the time of dismissal his symptoms again had responded only partially to treatment.

In 1951 the patient was hospitalized elsewhere, during which time a lung abscess and septicemia caused by a hemolytic Staphylococcus aureus developed. The abscess was drained surgically, and the septicemia was controlled with oxytetracycline (Terramycin®) therapy. For a short time he appeared to show some improvement but overwhelming sepsis developed and he died in shock despite supportive measures.

Necropsy did not reveal any significant gross findings except for some atrophy of the mucosa of the small intestine. Histologic studies disclosed atrophy of the small intestinal mucosa. Lymph nodes and bone marrow were not available for review.*

COMMENTS

The evidence for agammaglobulinemia in Case II was circumstantial, as electrophoresis was not performed. Fairly good evidence for its existence was present, however, in the consistently low values for total globulins; the fact that the patient experienced repeated infections, with death from generalized septicemia and a lung abscess; the absence of isohemagglutinins in the serum; and the absence of plasma cells in the bone marrow.

Figure 1 indicates the concentrations of serum albumin and globulin in 178 determinations on a series of 103 patients with non-tropical sprue recently studied by two of us (Green and Wollaeger [*11*]); the proteins were measured by the Kingsley procedure [*12*]. Each patient in the series had experienced symptoms of sprue for five years or more, the average duration being nineteen years. Quantitative fecal analysis for fat was carried out in all but five cases, and it invariably demonstrated the presence of steatorrhea. There was a high incidence of multiple, often severe nutritional deficiencies, as evidenced by the presence of anemia, advanced osteomalacia and hypoprothrombinemia with hemorrhage. This figure reveals that some patients had normal levels of serum albumin and reduced values for serum globulin; others showed the reverse, with reduced albumin and normal globulins, whereas still others had a reduction in both fractions. Low values for serum globulin ranged from 0.7 to 2 gm. per 100 ml. Since the gamma fraction normally comprises nearly half of the total globulin, it is probable that hypogammaglobulinemia was present in some of these cases.

TABLE I

ELECTROPHORESIS OF SERUM PROTEINS IN TWENTY PATIENTS WITH NON-TROPICAL SPRUE

Sex	Serum Proteins (gm./100 ml.)*					
	Total Protein (6.4–7.8)	Albumin (3.4–4.1)	Globulins			
			Alpha1 (0.3–0.4)	Alpha2 (0.6–0.7)	Beta (0.7–0.9)	Gamma (0.9–1.4)
F	5.5	3.4	0.48	0.75	0.64	0.27
M	4.9	2.7	0.32	0.59	0.80	0.43
M	5.5	3.2	0.33	0.73	0.79	0.43
F	4.6	1.9	0.53	0.67	1.02	0.54
F	5.9	2.3	0.68	0.96	1.30	0.66
M	4.9	2.7	0.35	0.56	0.66	0.65
F	4.7	2.3	0.37	0.63	0.78	0.65
F	5.4	2.9	0.37	0.66	0.74	0.72
M	5.3	2.7	0.37	0.60	0.87	0.74
F	4.3	2.3	0.31	0.36	0.48	0.87
M	5.2	2.1	0.50	0.87	0.77	0.95
F	5.8	2.8	0.49	0.77	0.80	0.95
F	5.6	2.3	0.47	0.94	0.94	1.03
F	4.6	1.4	0.46	0.74	0.94	1.12
M	6.2	3.1	0.40	0.63	0.86	1.20
F	6.3	3.1	0.42	0.64	0.80	1.27
M	4.3	1.1	0.60	0.57	0.54	1.47
M	5.7	1.9	0.48	0.88	0.92	1.55
M	7.6	3.7	0.38	0.67	1.09	1.79
M	5.2	1.4	0.44	0.63	0.58	2.15

* Figures in parentheses indicate normal ranges.

Table I shows the results of electrophoresis of serum proteins in twenty patients with non-tropical sprue. Nine of these had diminished concentrations of gamma globulin ranging from 0.27 to 0.74 gm. per 100 ml. The serum albumin was reduced in all cases, while the other globulin fractions were normal or increased slightly. From this limited experience it appears that when deficiencies of serum total globulin occur in non-tropical sprue they are caused by deficiency in the gamma fraction.

The high incidence of a sprue syndrome in reported cases of acquired agammaglobulinemia at once suggests the possibility that impaired absorption from the intestinal tract, with resulting nutritional deficiency, may be of etiologic significance in some instances of agammaglobulinemia. This possibility is supported further by our finding that significant degrees of hypoglobulinemia are not uncommon in non-tropical sprue and that abnormally low concentrations of the gamma fraction are responsible for much, if

* We wish to thank Dr. Gustave J. Dammin, of Boston, Massachusetts, for furnishing this necropsy report.

TABLE II

SERUM PROTEINS IN REPORTED CASES OF ACQUIRED AGAMMAGLOBULINEMIA ASSOCIATED WITH SPRUELIKE SYNDROME

Authors	Electrophoretic Analysis											Chemical Analysis (gm./100 ml.)	
	Total Protein (gm./100 ml.)	Per cent of Total Proteins					Gm. per 100 ml.						
		Albumin	α_1	α_2	β	γ	Albumin	α_1	α_2	β	γ	Albumin	Globulin
Sanford et al. [1]	*	*	*	*	*	0	*	*	*	*	0	4.1	0.6
Saslaw and Wall [2]	*	*	*	*	*	0–1.5	*	*	*	*	0	4.2	1.0
Rohn et al. [3]	*	53†	11†	21†	15†	0†	2.33†	0.48†	0.92†	0.66†	0†	4.0	0.37
Rosecan et al. [4]	5.04	55.4	9.8	17.5	17.3	0	2.8†	0.49†	0.88†	0.87†	0†	4.8	0.9
Barandun et al. [5]	6.0	71.1	5.3	11.8	11.8	0	4.26	0.32	0.71	0.71	0	4.7	0.7
Zinneman and Hall [6]	5.8	70.7†	20.7†		6.9†	1.7†	4.1	1.2		0.40	0.1	5.1	0.8
	5.7	60†	8.5†	17.5†	14†	0†	3.4	0.50	1.0	0.80	0.	*	*
Cooke et al. [7]	*	*	*	*	*	0	*	*	*	*	0.04	4	1.2
Kabler [8]	*	*	*	*	*	0	*	*	*	*	0	*	*
Huizenga et al. (present study, Case 1)	4.5	66	6.5	13.3	14.2	0	3.0	0.29	0.59	0.64	0	4.0	1.2

* No data for these fractions.
† Figures estimated from graph.

not all, of the reduction in total serum globulin in this disease. Those who have reported cases of agammaglobulinemia associated with a sprue-like syndrome generally have assumed that the absorptive defect was not responsible for the deficiency of the gamma globulin fraction of the serum. This assumption apparently was based on the expectation that defects in absorption would lead to a decrease in the other protein fractions, particularly albumin, whereas only the gamma globulin appeared to be greatly reduced in the cases in question. Table II summarizes the available values for serum protein in all the reported cases of agammaglobulinemia associated with a sprue-like syndrome, including our Case 1. By chemical methods, the serum albumin was normal in all instances, whereas the serum globulin uniformly was reduced. Electrophoretically, the serum albumin apparently was reduced slightly in three of the six cases in which values were given.

Another reason for the failure to ascribe etiologic significance to impaired absorption in agammaglobulinemia associated with sprue can be found in the clinical histories of some patients, which appeared to indicate that the symptoms of agammaglobulinemia preceded those of sprue. This has been true in only about half of the cases reported in the literature. In only one of our two cases did symptoms of sprue precede those of agammaglobulinemia. While such evidence is suggestive, its reliability is questionable, since the exact time of onset of either disease may not be ascertainable from the history. Evidence suggests that in patients with sprue an absorptive defect may precede by many years the onset of symptoms of sprue and may even exist from the time of birth [*11*]. Many cases of sprue can be traced to celiac disease in childhood, and it is possible that the number of such cases would be greatly increased if adequate information regarding infantile and childhood illnesses of these patients was available [*13–15*]. Patients with sprue may have relative clinical remissions, sometimes lasting many years, during which the intestinal function remains considerably impaired. Reduction in the synthesis of the various fractions of serum protein conceivably might take place in such patients even though symptoms of sprue were not apparent. This is exemplified by the third patient in Table 1. This patient had noted symptoms of sprue in 1939; however, at the time of the electrophoretic study in 1956 he did not have any symptoms related to sprue and was having one or two formed stools every day. Quantitative studies

revealed mild steatorrhea, with 13 gm. fat per twenty-four hours.

The plasma cells apparently have been established as an important source of the synthesis of antibody gamma globulin; although lymphocytes also may be concerned in this function, their role is not clear. The concentration of each protein fraction depends not only on the rate at which it is synthesized but also on the rate of its catabolism and excretion. This process of the formation and degradation of plasma proteins is extremely active [*16–20*]. In patients with agammaglobulinemia, available evidence indicates a failure of synthesis rather than excessive degradation [*21,22*]. This is supported by the normal half-life for tagged gamma globulin in Case I [*10*]. Further evidence to suggest failure of protein synthesis is the observation that patients with agammaglobulinemia do not have plasma cells in their tissues [*23*], a finding that was demonstrated in Case II.

The rate of synthesis of the plasma proteins no doubt depends on a number of variable factors, including the availability of the building blocks for protein, namely, the amino acids, as well as other substances of dietary origin, such as carbohydrates, fats, vitamins and minerals, which must be supplied to the body tissues in proper proportions. A deficiency of such nutrients might interfere with the production of various hormones and enzymes necessary for the normal synthesis of protein.

The production of hypoalbuminemia by means of prolonged semi-starvation has been observed frequently in human beings and experimental animals. Ordinarily, this is a reversible process that can be corrected by return to a normal diet. Only a few studies of the changes in the serum globulin fractions in states of semi-starvation have been carried out. Cannon [*24*] demonstrated that rats and rabbits made severely hypoproteinemic by diets low in protein but adequate in other dietary constituents exhibited a decreased tendency to form antibodies. Chow [*25*] reduced both serum albumin and globulin in animals by feeding diets deficient in either protein or calories.

Clinical studies related to alterations of serum protein in malnutrition secondary to starvation diets have been reported by Gounelle [*26*], Keys and associates [*27*] and others [*28,29*]. Gounelle noted a decrease in globulin without important modifications in the albumin in the serum of inmates of a French asylum and prison after they had been on a starvation diet for several months. Reductions in serum albumin occurred only in those who had edema caused by starvation. On the other hand, Keys' group did not find any significant alteration in the serum proteins of normal men subjected to a starvation diet for twenty-four to thirty-two weeks, nor did they note any increased susceptibility to infection. The differences between the results of these two studies might be explained by the fact that Gounelle's subjects were not in a good state of nutrition when the observations were begun. In fact, most of them had been interned for several years and had been suffering from chronic undernourishment for a long time. The increased restriction of food imposed by the war no doubt accentuated a pre-existing state of malnutrition. Prolongation of the period of semi-starvation of the subjects of Keys and co-workers might have resulted in a significant reduction in serum protein. Cannon, in his experimental studies, demonstrated that a considerable period was required to deplete the protein stores and reduce the function of antibody-forming tissues. As already noted, the average duration of the symptoms in the aforementioned patients with non-tropical sprue studied by Green and Wollaeger [*11*] was nineteen years, and all patients had experienced such symptoms for at least five years. Thus the opportunity for the development of a deficiency state of long duration is clearly apparent.

Limited observations are available in regard to alterations of serum proteins in non-tropical sprue. Aldersberg and co-workers [*30*] found an over-all depression of serum proteins, including both albumin and globulin, in a selected group of ninety-four patients who had non-tropical sprue. Albumin was affected to a greater degree than globulin. The serum of twenty patients was subjected to electrophoresis; the findings in general showed low values for albumin, whereas all twenty patients had normal or slightly increased amounts of gamma globulin. Litwins and Sang [*31*] reported a slight increase in beta globulin in three cases of sprue associated with sensitivity of the gastrointestinal tract to gluten. Cooke and associates [*7*], however, noted some diminution in gamma globulin, usually in conjunction with a general decrease in serum proteins, in a number of their patients with steatorrhea from various causes.

The question arises as to whether the changes in serum proteins in non-tropical sprue are

caused entirely by nutritional deficiency secondary to impaired absorption or whether other primary metabolic defects may exist in this disease. This question cannot be answered with complete certainty, but until now no other primary metabolic defect has been clearly demonstrated. All the abnormalities encountered in patients with sprue can be attributed reasonably to the impaired intestinal function invariably present. Therefore it appears likely that the pathogenesis of changes in serum proteins in sprue is similar to that in human beings and animals suffering from the effects of severe and prolonged undernutrition produced by inadequate dietary intake.

Gordon [*32*] and others [*33*] recently demonstrated that hypoproteinemia may result from loss of serum proteins into the gastrointestinal tract. Holman and associates [*34*] described a group of patients with hypoalbuminemia and hypogammaglobulinemia in whom albumin and gamma globulin disappeared rapidly from the plasma. These and other plasma proteins were found in the intestinal secretions by immunologic and radioisotopic technics. This suggested but did not prove that hypoproteinemia can result from excessive loss of protein into the intestine. Such a mechanism could be responsible for the reduced albumin and gamma globulin in some cases of sprue. However, this phenomenon did not occur in Case 1, since the half-lives of both albumin and gamma globulin were normal.

The increase in gamma globulin associated with clinical remission in Case 1 is further evidence that malabsorption may play a prominent role in the impaired synthesis of gamma globulin. This patient, like all the others in whom sprue and agammaglobulinemia have been associated, was considered to have an acquired form of agammaglobulinemia, which implies that the synthesis of gamma globulin was normal at some time prior to the onset of her illness. Therefore, it is reasonable to expect that the amount of gamma globulin could return toward normal coincidentally with improvement of intestinal function. However, to our knowledge, this is the first time that such a reversal has been reported in acquired agammaglobulinemia. Krebs [*35*] did note the return of the ability to form typhoid antibody in a patient who had agammaglobulinemia secondary to hypoproteinemia caused by malnutrition. While our patient still had hypogammaglobulinemia (0.28 gm. per 100 ml.) at her most recent examination, the amount was considerably greater than the generally accepted level for agammaglobulinemia, which is less than 0.1 gm. per 100 ml.

Considerable evidence indicates that gastrointestinal sensitivity to gluten has etiologic significance in many patients with non-tropical sprue and those with celiac disease. Good clinical remissions occur in a certain number of patients ingesting a gluten-free diet. One of our patients (Case 1) had a satisfactory clinical remission on such a diet, with return of normal bowel movements and a 30 pound gain in weight; however, she still has mild small intestinal dysfunction as manifested by slightly increased amounts of fat in the stool, and flat glucose and vitamin A tolerance curves. The roentgenologic state of the small intestine was greatly improved, but a minimal deficiency pattern persisted. This failure of small intestinal function to return completely to normal has characterized all the cases of sprue we have studied in which apparently complete and prolonged clinical remissions have been attained with a gluten-free diet [*36*]. The exact relationship between the clinical remission and the increase in serum gamma globulin in Case 1 cannot be assessed accurately at this time, but a cause-and-effect association must be considered a strong possibility. This patient had a serum gamma globulin of 0.18 gm. per 100 ml. before the gluten-free diet was instituted; this level may have been related in part to the administration of gamma globulin. At the most recent examination, however, she had not received gamma globulin for six months.

Zinneman [*37*] has suggested that a deficiency of pantothenic acid or pyridoxine might be responsible for the inability in Case 1 to synthesize gamma globulin, since it has been shown experimentally that the antibody response of rats with isolated deficiencies of these vitamins is markedly impaired. Subsequently Zinneman [*37*] administered pyridoxine empirically to one of his patients with agammaglobulinemia associated with steatorrhea without affecting the level of serum gamma globulin. This agrees with the results of Axelrod and Pruzansky [*38*], who found impairment in the synthesis of antibody gamma globulin but normal concentrations of serum gamma globulin in pyridoxine-deficient rats.

The alterations in serum proteins in the present two cases and in the series of Green and Wollaeger [*11*] indicate that impaired intestinal absorption may be a primary factor in patho-

genesis in some cases of agammaglobulinemia. Even when a history suggestive of sprue is lacking, it may be advisable to test for the presence of steatorrhea, since some patients with sprue do not complain of diarrhea and may exhibit only the evidences of secondary deficiency states, such as anemia, hypoproteinemia or osteomalacia.

SUMMARY AND CONCLUSIONS

A detailed study was made of two cases of agammaglobulinemia associated with non-tropical sprue. At least eight similar cases have been recorded.

Electrophoretic studies in twenty other cases of non-tropical sprue indicate that a reduction in serum globulin is not uncommon in this disease, either with or without an associated decrease in serum albumin. When deficiencies of serum total globulin occur in non-tropical sprue, the gamma globulin fraction is reduced.

A normal survival time for gamma globulin and albumin in the one patient with agammaglobulinemia in whom such a study was made suggests that the reduction of these fractions in the serum was not the result of excessive exudation of serum proteins into the gastrointestinal tract. Such evidence suggests the possibility that a nutritional protein deficiency secondary to impaired intestinal absorption in non-tropical sprue may be of etiologic significance in some cases of acquired agammaglobulinemia. In one of the two cases of coexisting non-tropical sprue and agammaglobulinemia, a significant increase in gamma globulin during a remission of sprue also appears to support this hypothesis.

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Antirheumatic Potency of Chemically Modified Adrenocortical Steroids*

EDWARD W. BOLAND, M.D.
Los Angeles, California

THAT seemingly minor deviations in the structure of adrenal cortical steroids may be accompanied by quantitative differences in their biologic activities was first suggested by the results of studies which compared the effects of cortisone and hydrocortisone therapy in laboratory animals. In 1945, four years before the anti-inflammatory property of cortisone was discovered, hydrocortisone, which differs from cortisone only in the presence of a hydroxyl instead of a keto substitution at the C-11 position of the steroid nucleus, was found to have greater physiologic activity. Results of muscle work tests, liver glycogen assays and regressive changes produced in the thymus and adrenal glands indicated that hydrocortisone was twice as potent as cortisone [*1,2*]. Moreover, twice as much cortisone as hydrocortisone was required to promote equivalent eosinopenic responses [*3*]. Subsequently, in 1951, hydrocortisone was shown to have greater antirheumatic potency than cortisone: by comparing the milligram doses required for the maintenance of equivalent clinical control of rheumatoid manifestations, hydrocortisone was determined as 30 to 50 per cent more potent [*4–7*].

In 1951 it was also noted clinically that the acetate esters of hydrocortisone and cortisone behaved differently [*8*]. When taken orally the antirheumatic potencies of cortisone acetate and cortisone (free alcohol) were found to be similar. Hydrocortisone acetate, on the other hand, was determined to be only half as potent as hydrocortisone (free alcohol). The lowered efficiency of hydrocortisone acetate on oral administration was attributed to its greater insolubility and poor absorption, features which later proved to be advantages for local intra-articular administration.

Since 1953 chemists have modified the molecular structure of hydrocortisone and cortisone in a variety of ways and by so doing have fabricated hundreds of synthetic steroid compounds. Many of these have exhibited differences in anti-inflammatory potency and/or selective amplification (or attenuation) of one or more biologic property. Of the changes that have been made in the structure of hydrocortisone and cortisone, the following have led to the development of compounds of direct or indirect therapeutic interest: fluorination at C-9 and at C-6; dehydrogenation at C-1–C-2 and at C-6–C-7; methylation at C-2, at C-6, at C-16 and at C-21; hydroxylation at C-16; and desoxygenation at C-21. Many analogues have now been fashioned by combining two or more of these alterations, and some of them have displayed unique biologic properties. Estimates of the antirheumatic potency of a number of these complex compounds will follow; but first it would seem appropriate to summarize, in general terms, the usual effect that each modification exerts when it is made singly.

INFLUENCE OF SINGLE CHEMICAL MODIFICATIONS ON ANTIRHEUMATIC POTENCY (FIG. 1)

Fluorination at C-9. In 1953, Fried and Sabo [*9,10*] discovered that the addition of halogen atoms at the 9 α-position of hydrocortisone caused enhancement of several biologic properties. Most significant was the fact that the potentiation did not apply with equal intensity to all metabolic effects of the hormone and that the biologic characters of the artificial compounds differed, depending on which halogen (chlorine, fluorine, iodine, bromine) was substituted. It became evident from these observations that the anti-inflammatory potency of the natural steroids could be increased and that

* From the Department of Medicine, St. Vincent's Hospital, and the University of Southern California School of Medicine, Los Angeles, California. This study was supported, in part, by a grant from the Ahmanson Foundation. Manuscript received October 14, 1960.

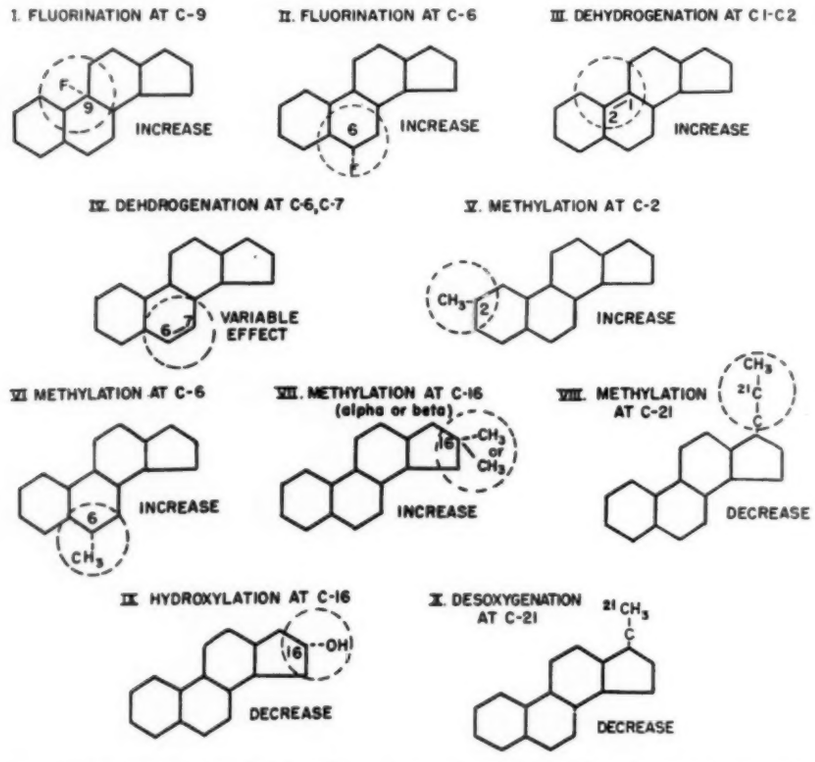

FIG. 1. Influence of certain individual structural alterations on antirheumatic potency (general).

certain of their other metabolic actions could be changed by modifying their chemical structure.

9 α-Fluorohydrocortisone (fluorocortisone) was found to be ten to fifteen times as effective as the parent hormone in promoting glycogen deposition and in suppressing the anti-inflammatory response in the rat, and it was fifty times more potent in retaining salt [*11,12*]. In rheumatoid patients its antirheumatic potency was determined to be ten times greater (on the average) than that of hydrocortisone, and by a similar factor it was more powerful in eosinopenic, ACTH-suppressing and nitrogen-wasting effects [*13,14*]. But the sodium-retaining and potassium-losing properties of the compound were augmented to an even greater extent, so much so that it could not be used systemically as an anti-inflammatory drug.

Fluorination at C-6. In general, compounds containing a fluorine atom at C-6 have exhibited intensification of anti-inflammatory, glycogen deposition and eosinopenic activities, although not to as great a degree as the 9 α-fluoro compounds. In contrast to 9 α-fluorination, the addition of fluorine at C-6 exerts little or no influence on electrolyte metabolism.

Dehydrogenation at C-1–C-2. The introduction of a double bond at C-1–C-2 positions of cortisone and hydrocortisone causes enhancement of anti-inflammatory potency and glycogen deposition, without a corresponding increase in electrolyte activity [*15*]. Clinical studies with prednisone and prednisolone, the delta$_1$ derivatives of cortisone and hydrocortisone, respectively, have demonstrated that their antirheumatic potencies are, on the average, about four times as great as those of the parent substances [*16,17*]. Furthermore, the potencies of the two analogues have been determined to be about equal, indicating that the presence of a hydroxyl rather than a ketone group at C-11 is not always associated with greater anti-inflammatory potency.

Estimates of the antirheumatic potency of several esters of prednisolone when administered orally to patients with rheumatoid arthritis have been made. (Table 1.) Differences in the solubility of these esters probably influenced alimentary absorption and the blood levels of active steroid and accounted in part for variations noted in the rapidity and duration of their effects. None of them proved to be more

TABLE I

PREDNISONE, PREDNISOLONE AND ESTERS OF PREDNISOLONE: ANTIRHEUMATIC POTENCIES AND CERTAIN BIOLOGIC ACTIVITIES

Activity Times Hydrocortisone in Animals			Antirheumatic Potency			
Compound	Granuloma Inhibition	Glycogen Deposition	Patients Compared (no.)	Potency Times Prednisolone (average)	Range of Potency Times Prednisolone (in individual cases)	Potency Times Hydrocortisone (average)
Prednisone*	3–4	4	24	...	...	3.9
Prednisolone*	3–4	4	20	...	...	4.0
Prednisolone, 21-tertiary butyl acetate†	3–4	3–4	8	0.9	0.8 to 1.5	...
Prednisolone, 21-aldehyde†	...	...	4	...	Ineffective in doses of 20 mg./day	...
Prednisolone, 21-phosphate†	3–4	3–4	6	0.75	0.6 to 1	...
Prednisolone, 21-azide†	1	1	5	0.15	0.1 to 0.2	...
Prednisolone, 17,21-oxide†	1	...	4	...	Ineffective in doses of 100 mg./day	...
Prednisolone, 21-bismethylene dioxide†	3–4	...	6	0.45	0.3 to 0.5	...

* Supplied by the Schering Corporation, Bloomfield, New Jersey, and by Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey.

† Supplied by Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey.

potent than prednisolone itself. Two highly insoluble compounds (the 21-azide and the 17, 21-oxide) were totally ineffective when taken in large total daily dosages. The antirheumatic action of one highly soluble ester (prednisolone 21-phosphate) was dissipated rapidly, and the average dosages required for comparable results were somewhat larger than those established for prednisolone; at least this was so when the two substances were administered in divided doses, taken three or four times daily.

Dehydrogenation at C-6–C-7. The placement of a double bond between the C-6 and C-7 position apparently does not produce a constant effect: this modification either eliminates or significantly decreases the anti-inflammatory activity of 11-keto steroids (cortisone series) but fails to influence anti-inflammatory potency or other biologic functions of certain 11-beta-hydroxy compounds (hydrocortisone series).

Methylation at C-2. Compounds containing a methyl group at the C-2 position have displayed distinctly altered biologic properties. In general, this substitution has selectively enhanced sodium retention and potassium waste of steroids containing an 11-beta hydroxy configuration (hydrocortisone series). The anti-inflammatory potency (by granuloma pouch assays) of 2 α-methyl-hydrocortisone has been adjudged 2.3 times greater than that of hydrocortisone. Unfortunately, the substance is too salt-retaining to permit appraisal of its antirheumatic activity in man.

Methylation at C-6. In contrast to the effects of methylation at C-2, the addition of a methyl group at the C-6 position does not aggravate sodium retention and potassium loss. Studies in animals suggested that 6-methylation might cause a substantial increase in anti-inflammatory potency. Gauged by granuloma inhibition tests, 6 α-methyl hydrocortisone was estimated to be three times as potent, and 6 α-methylprednisolone six times as potent as hydrocortisone. 6-Methyl hydrocortisone has not been assessed

clinically for antirheumatic potency. However, the results of clinical evaluations with 6 α-methylprednisolone indicate that 6 α-methylation enhances antirheumatic potency only slightly.

Methylation at C-16. In animal studies, compounds of both the hydrocortisone and cortisone series have displayed alterations in physiologic properties, including intensification of anti-inflammatory activity, when a methyl group was substituted at either the alpha or beta positions of C-16. Of the compounds with this substituent, tested in man, most have shown increased antirheumatic activity but the degree of increase has varied considerably. Methylation at C-16 reduces strikingly the marked salt retention produced by 9 α-fluorination.

Methylation at C-21. Recently compounds retaining a hydroxyl group at C-21, and methylated at this position, have been prepared. In general, this modification lessens anti-inflammatory potency and, like 16 methylation, strikingly reduces electrolyte activity, even of 9 α-fluorinated compounds.

Hydroxylation at C-16. The significance of this substitution rests in its ability to suppress rather than to enhance certain biologic functions. 16 α-Hydroxylation has uniformly lessened glucocorticoid potency and has reduced mineralocorticoid activity drastically. The modification was the first to make possible the systemic application of 9 α-fluorinated compounds as anti-inflammatory agents: because the substituent deprives 9 α-fluorohydrocortisone and 9 α-fluoroprednisolone of their excessive electrolyte effects while only partially reducing their strong antiphlogistic properties.

Desoxygenation at C-21. The removal of the oxygen side chain at C-21 diminishes the anti-inflammatory as well as the electrolyte activity of steroids. It does not, however, totally abolish anti-inflammatory activity and, therefore, contrary to earlier belief, the presence of a dihydroxyacetone chain at C-17 apparently is not a necessary requisite for anti-inflammatory action.

ANTIRHEUMATIC POTENCY OF CORTICOSTEROID ANALOGUES CONTAINING MULTIPLE CHEMICAL MODIFICATIONS

Estimates of the antirheumatic potency of thirty-two steroids containing two or more chemical modifications are submitted herein. For convenience of presentation the compounds are divided into five groups: 6-methyl, 16-methyl, 16-hydroxy, 6-fluoro and a miscellaneous group. Such a classification is entirely arbitrary and obviously is not entirely satisfactory because the individual substituents, although combined in different ways, are often duplicated. Data included in the accompanying tables which relate to antiinflammatory (granuloma inhibition), liver glycogen deposition or thymolytic activities were determined and made available by the research laboratories of the pharmaceutical company concerned in the development of the particular analogue. It is evident from a cursory perusal of these data that the results of biologic tests in animals cannot be translated reliably into terms of antirheumatic potency as estimated in patients with rheumatoid arthritis; at best, they allow only rough preclinical predictions of antirheumatic potency.

The potencies of twenty-seven of the thirty-two compounds were determined by me whereas the data on five analogues were obtained by other investigators. The method I employed for assessing antirheumatic potency was uniform throughout the study and consisted of treating patients with active rheumatoid arthritis first with an established steroid and then with the test compound and then determining the number of milligrams of each substance needed to maintain equivalent clinical improvement. Transfers of medication were made back and forth slowly (after a trial of two weeks or longer on each drug) in order to stabilize dosage and response with the test preparation. At least two sets of cross comparisons, and often three or four, were made in each patient. In most instances the new compound was compared with prednisolone. The potencies recorded in the tables represent averages for the groups studied.

6-Methyl Corticosteroid Analogues. In 1955, Hogg and co-workers [*18,19*] synthesized several 6 α-methylated analogues of hydrocortisone. Three of these have been administered systemically to rheumatoid subjects, and their antirheumatic potencies have been estimated. (Table II.) The potency of one compound, 6 α-methylprednisolone (methylprednisolone: Medrol®) was found to be somewhat greater (15 to 20 per cent) than prednisolone [*20*].

Two 21-desoxygenated compounds (6 α-methyl, 9 α-fluoro, 21-desoxyhydrocortisone and 6 α-methyl, 9 α-fluoro, 21-desoxyprednisolone) proved to have very potent anti-

TABLE II

6-METHYL CORTICOSTEROID ANALOGUES: ANTIRHEUMATIC POTENCIES AND CERTAIN BIOLOGIC ACTIVITIES

Compound	Activity Times Hydrocortisone in Animals: Granuloma Inhibition	Activity Times Hydrocortisone in Animals: Glycogen Deposition	Antirheumatic Potency: Patients Compared (no.)	Antirheumatic Potency: Potency Times Prednisolone (average)	Antirheumatic Potency: Range of Potency Times Prednisolone (in individual cases)	Antirheumatic Potency: Potency Times Hydrocortisone
6 α-Methylprednisolone (methylprednisolone)*	6	10.6	19	1.15	1–2	...
6 α-Methyl, 9 α-fluoro, 21-desoxyhydrocortisone (U-8390)*	56	25	...	...	...	1–2†
6 α-Methyl, 9 α-fluoro 21-desoxyprednisolone (U-8614)*	135	25	...	...	...	1–2†
6 α-Methyl, 9 α-fluoro prednisolone (U-8319)	116	24	Not adequately assessed clinically because of excessive salt retention†			

* Supplied by The Upjohn Co., Kalamazoo, Michigan.

† Data supplied by Dr. Hubert Peltier, The Upjohn Co., Kalamazoo, Michigan.

TABLE III

16-METHYL CORTICOSTEROID ANALOGUES: ANTIRHEUMATIC POTENCIES AND CERTAIN BIOLOGIC ACTIVITIES

Compound*	Activity Times Hydrocortisone in Animals: Granuloma Inhibition	Activity Times Hydrocortisone in Animals: Glycogen Deposition	Antirheumatic Potency: Patients Compared (no.)	Antirheumatic Potency: Potency Times Prednisolone (average)	Antirheumatic Potency: Range of Potency Times Prednisolone (in individual cases)
16 α-Methylhydrocortisone (MK-117)	3	2	21	0.65	0.3–1
16 α-Methyl, 9 α-fluorohydrocortisone (MK-126)	36	12	11	3.2	2.5–4.2
16 α-Methylprednisolone (MK-110)	16	5	7	1.3	1–1.7
16 α-Methylprednisone (MK-109)	12	3	15	1.1	1–1.3
16 β-Methylprednisolone (MK-148)	23	1.5	5	1.25	1–1.5
16 β-Methylprednisone (MK-129)	26	1	6	1.0	1.0
16 α-Methyl, 9 α-fluoroprednisolone (dexamethasone)	200	20	21	7.3	5–10
16 β-Methvl, 9 α-fluoroprednisolone (betamethasone)	70	11	9	6.5	6–8
16 α-Methyl, 9 α-fluoro, 21-desoxyprednisolone (MK-145)	20	4	6	1.25	1–1.6
16 α-Methyl, 9 α-fluoro, 6-dehydroprednisolone (MK-330)	150	6–7	11	6.8	5–10

* Supplied by Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey.

TABLE IV

16-HYDROXYL CORTICOSTEROID ANALOGUES: ANTIRHEUMATIC POTENCIES AND CERTAIN BIOLOGIC ACTIVITIES

Activity Times Hydrocortisone in Animals			Antirheumatic Potency			
Compound*	Glycogen Deposition	Thymus Involution	Patients Compared (no.)	Potency Times Prednisolone	Range of Potency Times Prednisolone (average)	Potency Times Hydrocortisone†
16 α-Hydroxyhydrocortisone (CL-19258)	0.4	0.3	7	...	...	0.4
16 α-Hydroxy, 9 α-fluorohydrocortisone (CL-16202)	6	2	9	...	...	3.0
16 α-Hydroxyprednisolone (CL-19380)	1	1	10	...	...	2.0
16 α-Hydroxy, 9 α-fluoroprednisolone (triamcinolone)	7	4	14	1.15	1.0–1.5	...
16 α-Hydroxy, 6 α-fluoro, 9 α-fluoroprednisolone (CL-36549)	28	19	12	2.3	1.8–2.5	...
16 α-Hydroxy, 6 α-fluoroprednisolone (CL-36548)	4	4	6	0.5	0.3–0.6	...

* Supplied by Lederle Laboratories, Pearl River, New York.

† Data supplied by Dr. Christopher Demos, Lederle Laboratories, Pearl River, New York.

inflammatory activity as gauged by the granuloma pouch technic in animals. But neither compound proved to be as active as prednisolone in rheumatoid patients (only one to two times as potent as hydrocortisone).

16-Methyl Corticosteroid Analogues. In 1957, Sarett and his collaborators [*21,22*] and Silber [*23*], synthesized a family of steroid compounds containing a methyl group at the C-16 position in common. Ten of these analogues have been tested for antirheumatic potency in rheumatoid subjects. (Table III.) In no instance did 16-methylation diminish the antirheumatic strength of the parent compound. In steroids not containing a 9 α-fluoro substituent, 16-methylation increased antirheumatic activity only slightly. An exception was 16 α-methylhydrocortisone (MK-117), the potency of which was estimated as 0.65 times that of prednisolone [*24*].

16-Methylation greatly amplified the antirheumatic potency (while greatly attenuating electrolyte activity) of each of five 9 α-fluoro compounds tested. 16 α-Methyl, 9 α-fluoroprednisolone (dexamethasone: Decadron,® Deronil®) was found to be, on the average, approximately seven times as potent as prednisolone in antirheumatic activity [*25–28*]. The drug is one of the most powerful antiphlogistic steroids that has been developed to date, and it is the only 16-methylated steroid that has had wide therapeutic application.

The influence of 16-methylation on antirheumatic activity appeared to be the same regardless of whether the substitution was made at the alpha or beta position. Three compounds (16 β-methylprednisolone, 16 β-methylprednisone, and 16 β-methyl, 9 α-fluoroprednisolone: betamethasone) exhibited about the same potency as their 16 α-counterparts. Historically these analogues were the first synthesized with a beta substituent (other than the 11 β-hydroxy of hydrocortisone) that have shown antirheumatic activity.

As demonstrated by 16 α-methyl, 9 α-fluoro, 6 dehydroprednisolone (MK-330), dehydrogenation at C-6–C-7 did not influence the antiphlogistic potency of dexamethasone.

The results of trials with 16 α-methyl, 9 α-fluoro, 21-desoxyprednisolone (MK-145) indicate that 21-desoxygenation greatly attenuates the antirheumatic strength of dexamethasone.

16-Hydroxy Corticosteroid Analogues. In 1956, Bernstein and his associates [*29*] and Fried and Borman [*30*], created several compounds containing an hydroxyl at the 16 alpha-position. Compared with the parent compound, each analogue that has been tested in animals has

TABLE V

6-FLUORO CORTICOSTEROID ANALOGUES: ANTIRHEUMATIC POTENCIES AND CERTAIN BIOLOGIC ACTIVITIES

Compound	Activity Times Hydrocortisone in Animals			Antirheumatic Potency		
	Granuloma Inhibition	Glycogen Deposition	Thymus Involution	Patients Compared (no.)	Potency Times Prednisolone (average)	Range of Potency Times Prednisolone (in individual cases)
6 α-Fluoroprednisolone* (U-7800: fluprednisolone)	8	81	...	13	2.6	2.3–4.2
6 α-fluoro, 16 α-methylprednisolone† (paramethasone)	50	150	...	12	2.8	2.5–3.5
6 α-Fluoro, 16 α-methyl* 9 α-fluoroprednisolone (U-10974)	730	165	...	9	7.8	5.0–9.3
6 α-Fluoro, 9 α-fluoro,‡ 16 α-hydroxyprednisolone (CL-36549)	...	28	19	12	2.3	1.8–2.5
6 α-Fluoro, 16 α-hydroxyprednisolone‡ (CL-36548)	...	4	4	6	0.5	0.3–0.6

* Supplied by The Upjohn Co., Kalamazoo, Michigan.
† Supplied by the Eli Lilly Co., Indianapolis, Indiana.
‡ Supplied by the Lederle Laboratories, Pearl River, New York.

demonstrated a drastic reduction in salt-retaining activity as well as in the anti-inflammatory strength of the parent compound [*31*].

One compound of the series, namely, 16 α-hydroxy, 9 α-fluoroprednisolone (triamcinolone: Aristocort,® Kenacort®) has been available commercially for four years and has been widely prescribed as an anti-inflammatory agent. Its antirheumatic potency was found to be slightly greater than that of prednisolone (about 15 per cent). The relative potencies of other 16-hydroxylated compounds recently studied are given in Table IV.

6-Fluoro Corticosteroid Analogues. Since 1958 several compounds containing a fluorine atom at C-6 have been prepared and tried clinically. Each of the analogues tested so far has shown substantially increased antirheumatic potency. (Table V.)

The antirheumatic potency of 6 α-fluoroprednisolone (fluprednisolone: Alphadrol®) was found, on the average, to be about two and a half times that of prednisolone. Long-term treatment studies with the compound indicate that it has no inclination to promote "new" peculiar biologic phenomena and, in contradistinction to 9 α-fluoroprednisolone, it does not aggravate salt and water retention. Observations made with 6 α-fluoro, 16 α-methylprednisolone (paramethasone) indicate that methylation at the 16 α-position may increase slightly the antirheumatic potency of 6 α-fluoroprednisolone.

The marked attenuating effect of 16 α-hydroxylation on antirheumatic potency was demonstrated clearly by two 6 α-fluoro compounds containing this substituent: 6 α-fluoro, 16 α-hydroxyprednisolone was found to be about half as potent per milligram as prednisolone, while 6 α-fluoro, 9 α-fluoro, 16 α-hydroxyprednisolone was found to be only 2.3 times as powerful as prednisolone.

Miscellaneous Corticosteroid Analogues. Among those corticosteroid analogues listed in the miscellaneous group two are of particular interest: 9 α-fluoroprednisolone and 21-methyl, 9 α-fluoroprednisolone. (Table VI.) Because 9 α-fluoroprednisolone contained two changes, each of which was capable of intensifying anti-inflammatory potency (a double bond at C-1–C-2 and a fluorine atom at C-9) it was not unexpected that the combination caused its antirheumatic activity to be multiplied (4.3 times that of prednisolone). But at clinically effective doses 9 α-fluoroprednisolone proved to be such a potent sodium-retaining agent that it could not be administered systemically as an

TABLE VI

MISCELLANEOUS CORTICOSTEROID ANALOGUES: ANTIRHEUMATIC POTENCIES AND CERTAIN BIOLOGIC ACTIVITIES

Activity Times Hydrocortisone in Animals			Antirheumatic Potency			
Compound	Granuloma Inhibition	Glycogen Deposition	Patients Compared (no.)	Potency Times Prednisolone (average)	Range of Potency Times Prednisolone (in individual cases)	Potency Times Hydrocortisone
9 α-Fluoro, 21-desoxycortisone (SC-5880)*	0.25	1	4	...	...	0.3
9 α-Chloro, 21-desoxyhydrocortisone (SC-5142)*	0.125	0.5	4	...	...	Ineffective in doses of 100 mg./day
9 α-Fluoroprednisolone†	25	42	6	4.3	3–5	...
9 α-Fluoro, 21-methylprednisolone (P-1742)‡	20	5	10	1.2	1–1.67	...
6 α-Fluoro, 9 α-fluoro, 21-methylprednisolone (P-1934)‡	40	100	9	1.3	1–1.79	...

* Supplied by G. D. Searle Co., Chicago, Illinois.
† Supplied by Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey.
‡ Supplied by Chas. Pfizer & Co., Brooklyn, New York.

anti-inflammatory drug. However, the addition of a methyl group at C-21, applied in such a manner that the dihydroxyacetone chain was not disrupted, resulted in the production of a compound which, though less active in anti-inflammatory activity, was nonetheless relatively free of salt-retaining properties [*32*]. 21-Methyl, 9 α-fluoroprednisolone was found to have slightly greater antirheumatic potency than prednisolone, and no clinical evidences of salt retention were noted in ten patients studied for short periods. Clinical observations and animal studies with this and other analogues containing the modification demonstrate that 21-methylation, like 16 α-hydroxylation, diminishes but does not eliminate anti-inflammatory activity. As is true with 16 α-hydroxylation and 16 α-methylation, the addition of a methyl radical at C-21 reduces sodium retention sufficiently to permit the systemic administration of 9 α-fluorinated compounds.

COMMENT

The development of synthetic analogues of hydrocortisone and cortisone which it is hoped will possess a wide dissociation between desirable and undesirable properties must be guided by information derived from studies of structure-function relationships. In the present communication an attempt has been made to correlate only one property, antirheumatic activity, with chemical structure. It is fully realized that the therapeutic efficiency of a steroid does not depend on its anti-inflammatory potency per milligram. Actually, enhanced potency alone means nothing unless it is accompanied by an absolute or relative decrease of one or more of those physiologic actions that lead to the development of unwanted effects. Nonetheless, the determination of a compound's therapeutic index must begin with a knowledge of its anti-inflammatory strength in terms of the number of milligrams a day required to uphold clinical improvement as compared to other steroids. Only when this has been established can an appraisal of its relative efficiency, i.e., maintenance of improvement in relation to the incidence and severity of undesirable reactions, on prolonged administration be undertaken.

It was hoped that information resulting from a compilation of data such as contained herein might serve as a basis for predicting the anti-

rheumatic potency of new steroids. However, this hope has not been fulfilled because the several chemical modifications discussed often promoted variable influences, especially when they were made in combination. Hence only rough estimates of potency are justified from theoretic calculations, and all too often these have proved to be erroneous. For example, the addition of a methyl radical at the C-16 position influences the antirheumatic strength of prednisolone only slightly but multiplies the potency when a 9 α-fluoro substituent is also present (as in dexamethasone). Conversely, 6 α-fluorination multiplies the antirheumatic potency of prednisolone about two and a half times but augments the strength of dexamethasone to a much lesser extent (6 α-fluoro, 9 α-fluoro, 16 α-methylprednisolone). (Table v.) The estimation of potency continues to depend, unfortunately, on laborious clinical trials.

Finally, it should be pointed out that as the formulas of effective and ineffective analogues have been compared during the past several years, the structural requirements for anti-inflammatory or anti-allergic activity have changed. Currently, the requirements may be stated as follows: a double bond between C-4 and C-5 in ring A; an oxygen atom at C-3, at C-11 and at C-20; and a beta-hydroxy group at C-17. So far these features have been present in every steroid that has effectively suppressed inflammation, although not every steroid possessing them has proved to be active.

SUMMARY

The antirheumatic potency of thirty-two analogues of hydrocortisone and cortisone was determined in patients with rheumatoid arthritis. Chemical modifications included: fluorination at C-9 and at C-6; dehydrogenation at C-1–C-2 and at C-6–C-7; methylation at C-6, at C-16 and at C-21; hydroxylation at C-16; and desoxygenation at C-21. Most of the compounds studied contained two or more of these modifications in various combinations. An effort was made to correlate chemical structure and the antirheumatic strength per milligram. In addition, data relating to the potencies of six different esters of prednisolone are presented.

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Review

Esophagogastrointestinal Leiomyo(sarco)mas*

E. R. N. GRIGG, M.D.

Chicago, Illinois

Leiomyoma is . . . (a tumour) composed of unstriated muscular fibre.
SYDENHAM SOCIETY LEXICON (1888)

A REPUTABLE bibliographic history of (alimentary) smooth muscle tumors would seem to require an introductory reference to the German father of clinical pathology, Rudolf Virchow (1821–1902): he was the first who surveyed this topic comprehensively, about one hundred years ago. In his classic account [*280*], Virchow stressed that myomas are most commonly found in the uterus, irrespective of pregnancy. Thereupon, he contended that the pregnant (hyperplastic) uterus was a sort of myoma [*141,279*], or rather, as it were, a myoma of sorts.

The comparison has a scent of oncologic heresy but there is no doubt about the histologic resemblance between myoma and healthy smooth muscle tissue. Indeed, not only "benign" but also "malignant" smooth muscle tumors, especially when originated in the walls of the gastrointestinal tract, display quite often a deceptively "innocent" cytologic make-up.

PROVENIENCE

These tumors may arise from any smooth muscle fibers in the body.

Among their odd starting points are the iris [*32*], a tendon sheath [*10*], a bronchus [*25*], the diaphragm [*185*], the kidney [*68*], the kidney capsule [*75*], the vagina [*250*], and the prostate (which may lead to vesical metastases [*234*]).

In the wall of the gastrointestinal tract, smooth muscle tumors originate from the muscularis mucosae, from the external muscularis, from isolated muscle fibers scattered in the submucosa or subserosa, perhaps also from vessel walls [*181*], similarly to what takes place in the skin (vascular leiomyoma).

Smooth muscle tumors have been recorded at all levels of the digestive canal. The first "congenital myom of the vitelline ductus" was described by the English pathologist Charles Barrett Lockwood (1856–1914): his specimen [*159*] came from a patient of the surgeon, and pupil of Paget, Thomas Smith (1832–1909). Patients with involvement of Meckel's diverticulum are no longer exceptional [*79,104,289*].

The first appendiceal myoma [*233*] was reported in Italy by Ugo Rosi (1862–1921), the second [*135*] in Philadelphia by the pathologist Aloysius Oliver Joseph Kelly (1870–1911). The digestive glands are occasionally the site of origin, e.g., the pancreas [*82*].

Exceedingly rare are locations near the upper end of the alimentary canal, such as in the pharynx [*255*] or mouth [*266*].

ONCOGENESIS AND MORPHOLOGY

Spontaneous slow-down, arrest (latency ?), various types of degeneration, even outright regression are frequently encountered in smooth muscle tumors [*167*]. Their oncogenic analysis reveals that, much like ontogeny repeats phylogeny, morphologic variants, heretofore described, are merely stages in development. (Fig. 1.)

Well circumscribed, seemingly (but never really) encapsulated, pinpoint to pea-sized nodules, consisting of properly differentiated, non-striated muscular fibers, are often found in the walls of the gut [*231*], stomach [*182,228*] and esophagus [*232,265*]. During such *interstitial* [*262*] stage, these miniature tumors are easier recognized by palpation than in any other way.†

† Many but not all the histopathologic statements contained in this paper (and over the years, so many others) have been "cleared" with, and through the always obliging courtesy of Prof. Paul Bernard Szanto, the chief pathologist of Cook County Hospital. But I alone am responsible for all the statements herein offered.

* From the Department of Radiology, Cook County Hospital, Chicago, Illinois. Manuscript received October 18, 1960.
NOTE: In accordance with the style of this Journal, the author's classic plurals have been converted to modernized plurals.

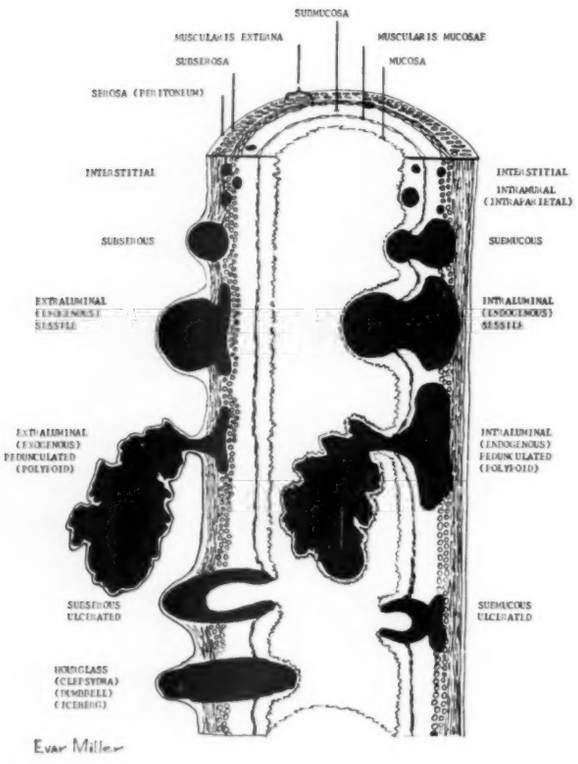

FIG. 1. The sectioned cylinder represents (schematically) a segment of the wall of the alimentary tract. Esophagogastrointestinal smooth muscle tumors have been given varied morphologic designations (such as interstitial, intramural or polypoid). Far from indicating different tumor types (aside from the two basic: intraluminal and extraluminal), these designations illustrate merely different developmental stages. (Drawing executed by Mr. Evar Miller, Art Institute, University of Illinois, Urbana.)

Most of these nodules, even those which grow, are of little clinical import [*57*]. When larger, while still asymptomatic, they tend to confuse the diagnostic issue, as they may be found by "accident" during operation or at autopsy [*178*].

Clinical instances of multiple smooth muscle tumors have been described in the esophagus [*108,219*], stomach [*134,174*] and intestines [*77,201*]. The potentially multicentric origin of myomas has been emphasized [*145*] by the French pathologist and medical historian Jean Joseph Alexandre Laboulbène (1824–1898).

MORPHOLOGIC DETAILS

While these tumors are still both *intramural* (intraparietal) and comparatively small, if actively growing, they may crowd their *submucous* location: the resultant pressure can erode the mucosa (*ulceration*), and thus open vessels (*bleeding*). The corresponding *subserous* (subperitoneal) type is also subject to intraluminal ulceration. These tumors may grow larger and still remain submucous or subserous [*170*]. More likely, peristalsis and other muscular contractions intrude (part of) the tumor, together with its mucosal cover, into the lumen of the alimentary canal [*90*], or extrude it beyond the level of the serosa. These two variants, whether *intraluminal* (endogenous) or *extraluminal* (exogenous), exhibit perforce a *polypoid* configuration, and thus become either sessile or pedunculated.

FIG. 2. With anamnesis dating back to the Fall of 1894, a thirty year old woman, who had a large umbilical mass, was operated on December 3, 1896, by von Eiselsberg (in Vienna). This 5.5 kg. "fibromyoma" was the first successfully excised exogastric smooth muscle tumor [*70*]. (Reproduced through the courtesy of the John Crerar Library, Chicago.)

In the stomach the two variants are called *exogastric* and *intragastric:* they had been described by Virchow who called them external and internal [*280*]. The exogastric type seems to be more spectacular and has provoked many case reports [*31,95,157,196,221,258*]. (Fig. 2.)

The extraluminal variety grows practically unimpeded, and has been known to reach monstrous sizes, whether in the esophagus [*160*], stomach [*38*], jejunum [*262*] or rectum [*253*]. When originated in the gut, it may "fill" the abdominal cavity to the point where the site of its actual inception becomes unrecognizable, as in the autoptic instances (age of patients: one and a half [*136*] and four [*137*] years), seen by Joseph Vincent Kelly (1844–1918) of Philadelphia.

When found in the properitoneal space, a smooth muscle tumor is usually not of gastrointestinal origin but of genital origin, as it may have come from the

round ligament [*263*], while from the urinary tract it would expand into the retroperitoneal region [*302*].

Simultaneous intrusion and extrusion occurs rarely. It is called the *clepsydra* (hourglass, iceberg, or dumbbell) type, and has been described even in the esophagus [*168,265*].

Spontaneous peranal expulsion of (fragments of) smooth muscle tumors is not an exceptional occurrence. It is in part due to their relatively loose attachment.

The Danish-born Chicago pathologist and surgeon, Christian Fenger (1840–1902), whose exploits are part of the tradition in Cook County Hospital, removed successfully a "myomyxofibroma" from the ileum of a seventy-five year old man, and described it as "so benign and so little attached that it comes out easily" [*83*]. Facile enucleation is often the case also in the esophagus [*218*], stomach [*208*] and rectum [*41*].

When pedunculated, smooth muscle tumors may grow into huge, fungating masses. Localized areas of necrosis will detach fragments which, when the tumor is extraluminal, fall into the peritoneal cavity. When it is intraluminal the fragments are evacuated with the alvine stream.

Cystic degeneration of smooth muscle neoplasms occurs occasionally, even in the jejunum [*44*]. Usually these tumors are solid and well demarcated, but have no true capsule. They *calcify* quite frequently [*150*], partly because of intratumoral bleeding.

ASSOCIATION WITH OTHER DISEASES

Smooth muscle tumors of the gastrointestinal tract reveal neither synergy with nor antagonism toward other diseases. Associations are on record between smooth muscle neoplasm in the esophagus with squamous cell carcinoma of the thymus [*93*], in the stomach with gastric adenosarcoma [*51*], gastric carcinoma [*256*] and pancreatic carcinoma [*238*], and in the intestines with cutaneous fibromata mollusca [*77*].

COMPLICATIONS

Exsanguination [*7,131,184*] is one of the redoubtable hazards of smooth muscle tumors of the gastrointestinal tract.

In one instance bleeding continued for fourteen years; the site of bleeding (a jejunal tumor) was overlooked at gastrojejunostomy, and the patient finally died from massive hemorrhage [*113*]. In extraluminal varieties death may result from fulminant intraperitoneal bleeding [*188*]. As a matter of fact, a deadly red leiomyomatous streak [*80,138,158,183,194, 200*] marks the history of these tumors.

Another ever-present danger is *obstruction*, from incomplete, or transient, to total occlusion.

Obstruction is not restricted to intraluminal forms: the larger intramural tumors [*139*] may give it. An antral smooth muscle tumor may simulate pyloric stenosis [*215*], just as it may cause gastroduodenal intususception [*16*], or "invagination" in the small intestine [*87*].

Superficial secondary *infection* is not uncommon, but it seldom leads to overt suppuration [*18*]. *Fistulization* is said to occur somewhat more often [*175*] than *perforation* [*20*].

An antral smooth muscle sarcoma perforated into the epigastric subcutaneous tissues, which resulted in fatal gas gangrene [*140*]. In another patient, with a more protracted course, the presenting symptom was suppurative arthritis of the right knee, first noticed on November 10, 1923. This was followed by various septic episodes, and death occurred in Cook County Hospital on January 24, 1924. Autopsy revealed that the septicemia originated from a perforated exogastric myoma. The preceding case history [*292*] was reported by Harry Gideon Wells (1875–1943), the chemical pathologist and biophilosopher from the University of Chicago, at a time when their staff had not yet renounced privileges at Cook County Hospital.

A unique occurrence, seen in Vienna, was that of a seventy year old woman with huge exogastric myosarcoma perforated through the duodenum into the gallbladder; massive hemorrhage was the cause of death [*284*].

Smooth muscle tumors of the gastrointestinal tract may be very "benign" [*5*] or "innocent" in appearance [*283*], but they are in reality quite wicked.

NOMENCLATURE

The names given to smooth muscle tumors in the universal literature (cf. references) are almost as varied and confusing as modern psychosomatic definitions. Proper understanding demands a bit of semantic history.

Polyp, in Latin *polypus*, comes from the Greek word for octopus, meaning many-footed. The classics applied its medical connotation exclusively to nasal polypi; in the Hippocratic Canon appears the older form πόλυπος [*120*], as well as πώλυπος [*121*].

The origin of the word, and the continuing synomymy, were explained by the first century Roman science writer, Aulus Cornelius Celsus: both the nasal and the sea polyp have smooth-walled flesh and several roots (respectively tentacles) [*48*], al-

though the latter is a rare occurrence in "medical" polypi.

The term sarcoma comes from the verb σαρκόω, to make fleshy. Its first recorded utilization occurs in the medical definitions of the great systematizer Galen who, writing in Greek in second century Rome, specified that σάρκωμα (sarcoma) is abnormal flesh growing in the nostrils. Thus, Galen's polyp (he employed the Attic form πολύπους [*96*]) was by definition a sarcoma, but not all Galenic sarcomas were polypi; the distinguishing features were size and shape! This pathogenetic relationship between sarcoma and polypus, reiterated [*211*] in the seventh century by the Byzantine surgeon Paul of Aegina, was carried into the Renaissance [*99*].

Among the many nasal polypi, called sarcoma for longer than one millenium, a certain number must have been of smooth muscle origin, just like the leiomyosarcoma [*65*] removed by Dobben with a snare from the floor of the left nasal choana.

Toward the end of Medieval times, autopsies were more frequently performed; "polypi" were thus revealed in many other parts of the body. Indeed, the term itself was often abused, e.g., well into the eighteenth century, intravascular blood clots were also called polypi [*36,99*].

In Maria Theresa's Vienna, the commentator Gerhard van Swieten (1700–1772) equated the word sarcoma with uterine polyp [*269*]. Soft polypi were called (since Galen) meaty polypi (*fleischige* in German, *charnus* in French, *carnosi* in Italian). In London, the celebrated William Hunter [*129*] (1718–1783) meant by fleshy (i.e., sarcomatous) tubercles, the tumors which bulge at the surface of the uterus.

Beginning with Galen, and through the early nineteenth century, *sarcoma* (and softness) carried a benign connotation. The notion of malignancy was monopolized by *carcinoma* (and hardness), derived from the verb καρκίνόω, which meant to become (as hard) as a crab. The idea of "soft malignancy" was introduced by the English surgeon John Abernethy (1764–1831), who classified [*1*] the *genus sarcoma* into several varieties, for which he is remembered with an eponym (Abernethy's liposarcoma). Finally, in 1847, Virchow added cytologic baselines for the grouping of sarcomas.

In 1803 (two years after being granted a medical degree in Paris), the brilliant Gaspard Laurent Bayle (1774–1816) re-christened those uterine nodules (Hunter's fleshy tubercles) *corps fibreux* [*21*]. The term became very popular, both in France and in England; for instance, the London surgeon Prescott Gardner Hewett (1812–1891) called what must have been smooth muscle tumors "fibrous polyps" [*119*].

In Berlin, during the 1830's, a neuroanatomist, Johannes Peter Müller (1801–1858), created a synonym from the Greek etymon δεσμός (meaning bond) and came out with *tumor fibrosus seu desmoides* [*198*]. Both designations are still in active use (fibrotic or desmoplastic reaction).

Very popular became the appellation *fibroid*, coined (for the uterus) by the Austrian father of clinical pathology, Karl von Rokitansky (1804–1878). He used it accurately (albeit without microscopy) to designate an esophageal smooth muscle tumor [*230*].

The term *myoma* was first employed by Virchow in 1854 in the combination *myoma teleangiectodes*, meaning the gravid uterus [*279*].

In a communication dated June 1855, the surgeon and pianist Albert Christian Theodor Billroth (1829–1894), by taking Virchow as reference, described a *myoma cysticum* [*26*] (which years later turned out to be a myxosarcoma). In 1858, August Förster (1822–1856) applied the term myoma to a gastric smooth muscle tumor [*91*]. He then described a *fibroid of the ileum* [*92*] (the first histologically authenticated smooth muscle tumor in such location), and proposed the name myoma also for the latter. This drew thunders from Virchow who, being the editor of "his" *Archiv*, appended to Förster's paper [*92*] a sputtering footnote (on p. 271), calling attention to the fact that he (Virchow) had originated the term myoma in 1854 [*279*].

In a booklet [*301*] on typhoid fever, published in 1864, Friedrich Albert von Zenker (1825–1898) proposed the term *leiomyoma* (from λεῖος, smooth) for smooth muscle tumor, and *rhabdomyoma* (from ῥαβδωτός, striped) for striated muscle tumor.

Virchow's classic account on myomas was delivered in part as a lecture to medical undergraduates in Berlin on February 28, 1863. In the published version, printed without date [*280*] (presumably in 1866), Virchow introduced Zenker's proposed terminology, only to reject it. He offered instead corresponding Latin etymologies, i.e., myoma *laevi-cellulare* and myoma *strio-cellulare* [*280*]. Virchow failed in this promotion of Latin etymons. In 1862 the first German edition appeared of a famous textbook of pathology by Johann Paul Uhle (1827–1861) and Ernst Leberecht Wagner (1829–1888). Both the first and the second (1864) editions contained the word myoma, to which leiomyoma was added beginning with the third (1865) edition [*285*], i.e., before the publication of Virchow's classic account [*280*].

An English translation of Wagner's textbook (from the sixth German edition) appeared in 1879. It carried the following line, significant for the terminologic muddle, created by the symbiosis of "French" and "German" catchwords: "Tumor of smooth

muscle fibres (myoma, leiomyoma, fibromyoma, fibroid in the narrower sense, myo-fibroid)" [*286*]. As a matter of fact, Albert Hénocque had inserted the term *léiomyome* in the *Dictionnaire des Sciences Médicales* which was published in Paris in 1869.

As a corollary to Virchow's cellular view of oncogenesis, most pathologists label a tumor after the type cell from which it arises, regardless of the degree of secondary proliferation of stroma [*254*]. A tumor composed of pure muscular tissue is soft. When it is harder, this means that connective tissue is taking over. Occasionally, there may be some difficulties in finding (on microscopy) muscular remnants, needed for identification of its true neoplastic origin.

In the presence of overwhelming stroma, some observers tend to preserve a "fibrotic" reminiscence in the tumor's denomination. Thus, in eclectic South America, one may encounter the term *leiomiofibroma* [*248*].

In 1901, in Paris, Jean Heitz (1876–?) thought that *liomyome* [*116*] (without *e*) sounded better He had at least one follower in this country, the Irish-born, Rush-educated, Brooklyn proctologist Jerome Morley Lynch (1870–1951) who bred a baleful of (contracted) *liomata*, including *liomyoma*, *liomyoblastoma*, and *liomyosarcoma* [*167*].

In the past century, few new terms were offered, such as the Belgian *myoïde* [*41*]. Some of Virchow's pet appellations were continued in use [*162,293*]. Billroth's *cystomyoma* was once revived [*44*], then re-circulated, after a four-decade interval [*85*].

In this century, shades of Müller flickered when the Kansas City surgeon George Morris Gray (1856–1912) reported a "desmoid in the stomach" [*107*].

As of today, leiomyoma, with its transliterations and sarco-derivates, is the accepted vocable, world-wide. This includes not only the United States and Western Europe (from Belgium [*289*], France [*160*], and Germany [*282*], to Great Britain [*69*], the Netherlands [*108*] and Scandinavian countries [*294*]), but also Latin America (e.g., Argentina [*4*], Brasil [*45*] and Cuba [*73*]), Soviet Russia [*272*], a satellite (Hungary [*234*]), the antipodes (Australia [*197*] and New Zealand [*296*]) and Japan [*132*].

(PRE)HISTORIC LEIOMYO(SARCO)MAS

The history of smooth muscle tumors is said to begin with Virchow. Very few retrograde reviews [*189,262*] reach beyond that point (except for inserting a few exotically obsolete references).

Retrospective diagnoses are inherently debatable. One must accept (or reject) them—in the words of the Montevideo surgeon Carlos Stajano—*sin* (without) *mayores garantias:* indeed, some of the historic cases [*260*], which he considered gastric neuromas, were probably of smooth muscle origin!

Search for a classic citation elicited a verse by Horace (65–8 B.C.):

Illuc praevertamur, amatorem quod amicae
Turpia decipiunt caecum, *vitia aut etiam ipsa haec*
Delectant, veluti Balbinum polypus *Hagnae.*

The passage (unfortunately !) does not refer to cecal polyp. It is from the friendship satire (*Satires* i, 3, 38–40), dedicated to Maecenas, and merely stresses that a lover is blind (*caecum*) for his loved one's ugly features (*turpia*) so that her defects (*vitia*) delight him just as Hagna's polyp delighted Balbinus.*

The vocables *polyp* and *intestine* met just as fortuitously in a quote [*220*] from Pliny the Elder (23–79 A.D.), as he discusses the single orifice of the sea polyp's intestine. In another passage, Pliny might have implied that nasal polypi could ulcerate.

At this point, the futile (pre-)historic search shall be closed. Instead, (post-)Renaissance cases will be listed (mostly with autopsies), by organs.

ESOPHAGUS

An otherwise excellent American review paper [*265*] of 1956 grants a 1559 date to the (earliest ?) report of esophageal polyp, attributed to Sussius (with double s).

The citation was traced through a British article [*86*] of 1953 and an Estonian monograph [*189*] of 1895 to the prize essay [*99*] of 1833 written by the French anatomophysiologic external pathologist (i.e., surgeon) Pierre Nicholas Gerdy (1797–1856). The origin of the Sussius quotation proved to be the inaugural thesis (on nasal polypi), sustained not in 1559 but in 1743 by Johann G(eorg ?) Süss† (1718–?) in Witten-

* Horace referred to nasal polyp also in his imprecational epode (*Epodes* xii, 5), which is a filthy alcove conversation, and was therefore expurgated (together with the eighth epode) from many prudish editions. That passage attributes a fetid odor to nasal polypi, perhaps by confusion with ozena, which takes its name from the Greek word (*οζαινα*) for a smelly coelenterate. Two centuries later Galen was to define polyp and ozena in the same paragraph [*97*].

† An Italian phlebotomist, Giovanni Battista Susio (1524–?), whose Latin name was Susius (with single s), composed the often reprinted *Liber sanguinis mittendi ratione*. Its second edition (Basle, 1559) must have been at the origin of the 1559 date, which first appeared in the article by Geoffrey Flavell [*86*] (not in Minski [*189*]). Crerar had no copy of Susio's "bloody" opus, but Prof. Dorothy Schullian, from the Historic Branch (Cleveland) of the National Library of Medicine, graciously offered for perusal the *princeps* edition (1558); as expected, it contained no mention of esophageal (or of any other kind of) polyp.

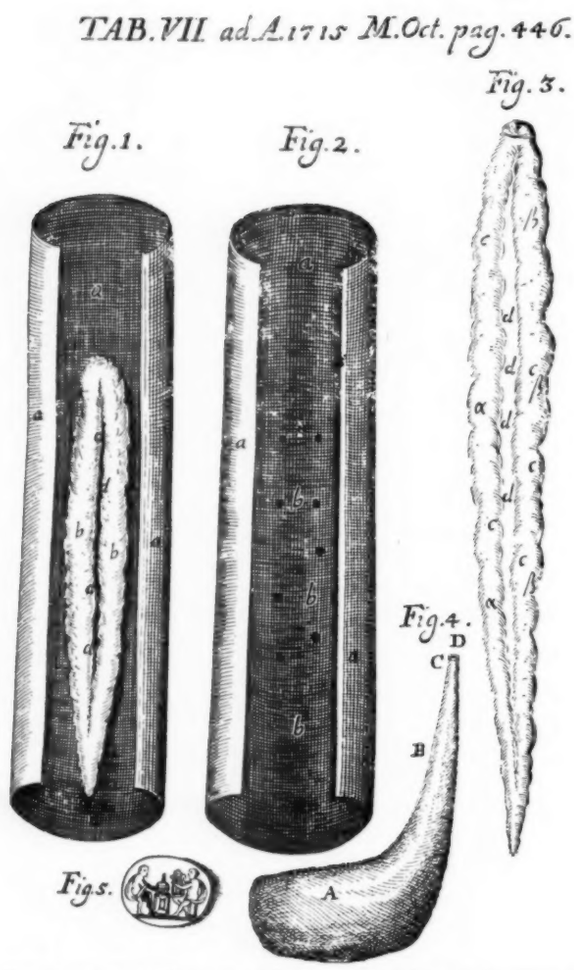

FIG. 3. A forty-three year old male patient, who complained of swallowing difficulties, was seen by a *rustic medicaster* (a derogatory term for country practitioner). An attempt was made to pass a *peniculum ventriculi* (ingestion of sponge, attached to a string, for subsequent withdrawal), but the "instrument" would not pass into the stomach. Progressive starvation turned the formerly obese patient into a virtual skeleton (τῷ σκελετῷ). The autopsy, performed by Schmieder [*246*] in April 1715, revealed an intact stomach (4A). The dilated esophagus (4B) contained a large polyp (1b), adherent to the posterior wall: after its removal (3) the insertions became visible (2b). The Bacchic coin scene (5) depicts two merry companions, one with harp, the other with a bottle, while underneath the bottle appears a (symbolic?) hourglass. (Reproduced through the courtesy of the John Crerar Library, Chicago.)

berg (Saxony) [*268*]. His patient had suffered from emaciating dysphagia; the autopsy revealed a lengthy, worm-like polyp, which extended (allegedly) from mid-esophagus to the pylorus.

Thus far, the earliest authenticated case history of esophageal polyp was reported in 1715 by Sigismund Schmieder (1685–1717), who included also drawings:

D. SIGISMUNDI SCHMIEDERI,
Academ. Carolino - Imperial. Naturæ Curiosorum
Socii, & Practici Lommacensis,

SCHEDIASMA

Curiosum Pathologico-Medicum
De
POLYPO OESOPHAGI VERMIFORMI RARISSIMO,
à
Quotidiano Pulveris sternutatorii Hispanici, vulgò
Spaniol / abusu progenito,
cum figuris æneis.

DELITII
Apud CHRISTIANUM VOGELGESANGIUM, Typogr.
M DCC XVII

FIG. 4. This first book(let) on esophageal polyp (*cf.* Fig. 3) was printed two years after the 1715 paper in the *Acta Eruditorum* [*246*]. The *D.* (before Sigismundi) stands for *Dominum*, meaning Mister. The subtitle intimates that the polyp may result from daily abuse of sneezing powder: the tobacco was called *Spaniol* because Spaniards had introduced it from the New to the Old World. (Reproduced through the courtesy of the National Library of Medicine, Washington, D. C.)

The patient, a forty-three year old man named Johann Gottfried Grosse, died after experiencing progressive dysphagia. The autopsy (Fig. 3) showed a soft, fleshy, fibrillous polyp, which filled the distended esophagus [*246*]. This observation was also published as a separate tract (another first). (Fig. 4.) In 1760, Haller reprinted it in one of his collections.

The first recorded successful removal of such an esophageal polyp was performed by the Swiss practitioner Johannes Hofer (1669–1752). (Fig. 5.)

The patient was a fifty-five year old nun who had complained of dysphagia on and off since 1743. On September 14, 1746, she "brought up" a dark bluish polyp which she grabbed with her teeth, while its pedicle was still attached somewhere in the "throat." Next day, Hofer extracted the polyp with a forceps, there was a small hemorrhage, but the patient made a full recovery (she died three years later of "peripneumonia") [*123*].

Only transient relief was achieved, in a fairly advanced stage, by Dallas, a Scottish surgeon [*60*].

The sixty-eight year old James Davison entered the Royal Infirmary (Edinburgh) on April 9, 1763. He could eructate at will a large, fleshy excrescence. His other major complaint was dysphagia. On May 15,

Dallas cast a noose on this esophageal polypus (a ligature passed through a hollow ring, to which a long stalk was connected) and amputated (part of) the tumor. The severed portion was subsequently discharged through the stool. The patient had recovered from the operation when Dallas presented the case in 1764 to the Philosophical Society of Edinburgh [*60*]. Dallas died in that same year. The patient returned to the Infirmary to die in April of the following year (1765). The autopsy, performed by Alexander Monroe, II (1733–1817), demonstrated a huge esophageal polyp, assumed to have regrown (at least partially) since the operation [*190*]. (Fig. 6.)

Quite remarkable, chronologically, was the patient operated upon by Albrecht Theodor Middeldorpf (1824–1868), a surgeon from Breslau.

Joseph Jänsch, a forty-two year old shepherd, "retched up" a reddish blue, "highly vascular" polyp. On January 14, 1853, Middeldorpf hooked the polyp, threw a ligature (connected to a string) around it, and severed the distal portion (of the polyp) with a knife. The patient swallowed the stalk (the string came loose after eighteen days); when seen four and a half years after the operation, he was still asymptomatic. Histologic examination of the specimen disclosed smooth muscle fibers within the tumor

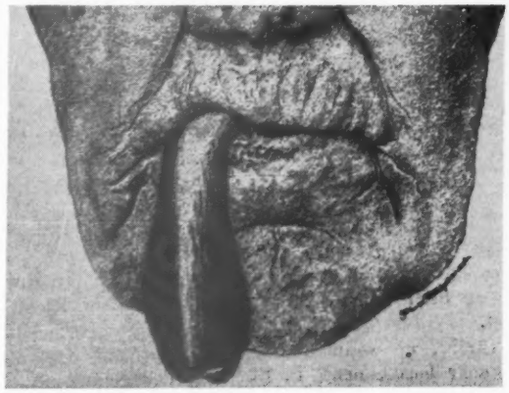

FIG. 5. In 1746 a polyp (very similar to the one reproduced herein) was successfully removed by Hofer from the "throat" of a nun [*123*]. In a 19th century case, the patient, Trina Schmidt, was a sixty-five year old peasant, and the polyp "came up" eight days before it was separated, on May 9, 1891, from its esophageal base, and extracted by the surgeon Wilhelm Koch (of Dorpat). The 14 cm. polyp was a leiomyoma. The puckered spot, shown in the drawing at the place where the polyp touches the lower lip, was a squamous cell carcinoma (excised a few months afterwards). The drawing is reproduced from the first literary review (dated 1895) on esophageal polypi [*189*], which is quite comprehensive, although it failed to mention Hofer [*123*]. (Reproduced through the courtesy of the Medical Library of the University of Illinois, Chicago.)

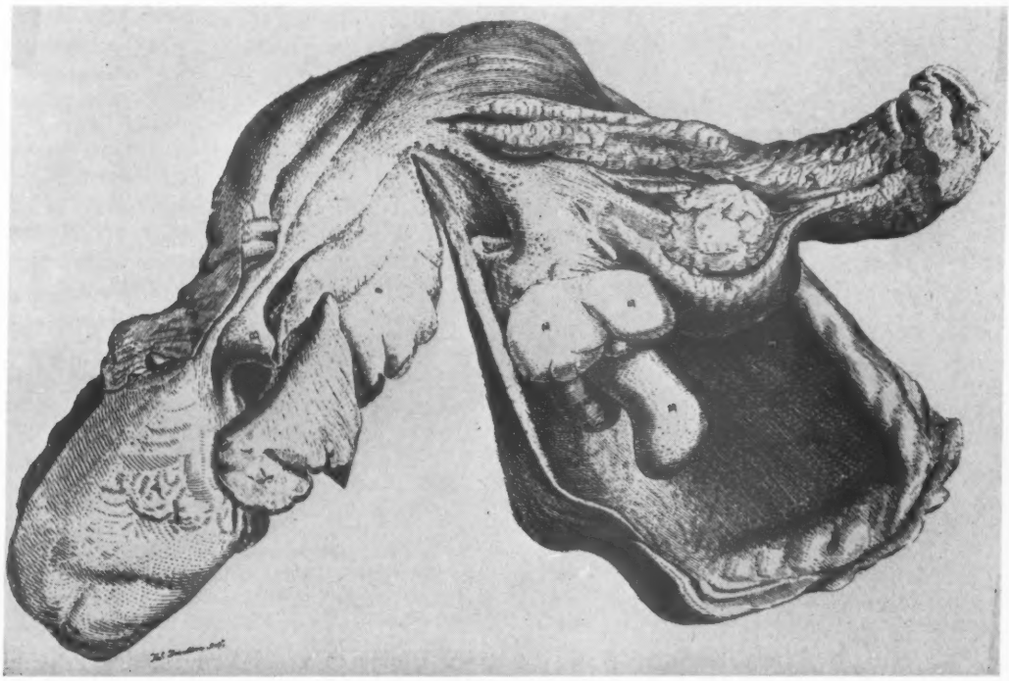

FIG. 6. The original caption, prepared by Monro [*190*] for this venerable woodcut of 1765, executed after an autoptic specimen of esophageal polyp, reads as follows: A, tongue; B, epiglottis: CC, dilated esophagus cut open; D, root of the polypus; EEEE, lobes into which the polypus was split; F, cicatrix where Dallas had applied ligature (*cf.*, Dallas [*60*] and text). (Reproduced through the courtesy of the John Crerar Library, Chicago.)

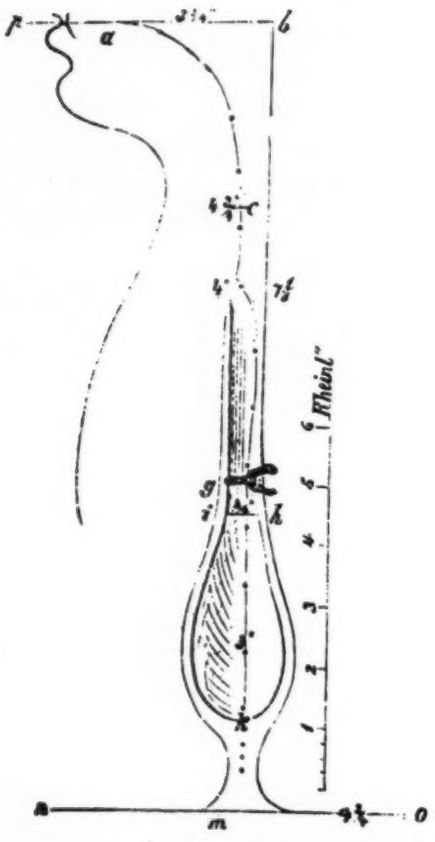

FIG. 7. On January 14, 1853, Middeldorpf ligated and transected an esophageal polyp, which had been temporarily "regurgitated" by the patient. The operation was a complete success (four and a half years follow-up). Histologic examination of the specimen revealed numerous smooth muscle fibers (this is chronologically the first authenticated instance of esophageal leiomyoma) [*187*]. Based on measurements performed on cadavers of the approximate size of the patient's body, Middeldorpf reconstructed graphically the size (length) and location of the polyp. (Reproduced through the courtesy of the Medical Library of the University of Illinois, Chicago.)

[*187*]. This, then, was the first microscopically authenticated esophageal leiomyoma. (Fig. 7.)

A report of Virchow's first esophageal case (preparation No. 37 from the year 1856) was published in 1857 in the inaugural thesis [*235*] of his pupil Carl Friedrich Ferdinand Runge (1835–1882). The case reported in Belgium by Octave Lesueur (1802–1860) was published in 1850 [*152*], but it had no histologic authentification.

After reading Middeldorpf's paper [*187*], Jakob von Roeser (1799–1862), who described incarcerated obturator hernia, recalled that he, too, had "cured" a dysphagic and dyspneic thirty-six year old brewery worker: On August 19, 1826, Roeser had used pincers to tear out an apple-sized "fibroid" from the patient's throat. The patient was alive and well in 1850 [*229*].

Intramural tumors of the esophagus had also been reported.

In 1677, Steven Blankaart (1650–1702), an Amsterdam practitioner, performed an autopsy on a patient and found that a "steatoma" of the esophagus had caused his death by starvation [*28*]. A similar case was seen before 1685 by Johann Ludwig Hannemann (1640–1724) in Kiel [*112*]. In 1777, in Metz, Helian performed an autopsy on a sixty year old man, who had died after several years of swallowing difficulties, and found a hard tumor sandwiched between the second and the third coats on the posterior wall of the esophagus at the level of the tracheobronchial bifurcation. Helian's case report was sent to Paris by the Royal Medical College of Nancy [*117*].

As a bonus feature will be quoted the fact—based on the authority of the very learned Alfred Armand Louis Marie Velpeau (1797–1867) [*276*]—that a French veterinarian, Dandrieu (from Lavardac), enucleated an egg-sized intraparietal tumor from the esophagus of a ram; the "patient" made a full recovery in eighteen days (about 1805).

STOMACH

A very early reference in this group is of indirect nature. It appears in the report of a transient (emetic) medical cure of a twenty-five year old housewife. The case was reported by the famous Marrano physician João Rodriguez de Castello Branco, *alias* Amatus Lusitanus (1511–1568), who theorized that the patient's epigastric swelling must have been caused by a fleshy excrescence, hanging from the stomach's mouth (*carnea excrescentia, ab ore ventriculi pendente*) [*6*]. This statement indicates knowledge gained from a previous (presumably autoptic) experience, but that earlier source could not be traced.

Gastric polypi tend to prolapse into the pylorus, as is to be expected in the presence of peristalsis. In Paris, the anatomopathologist Gilbert Breschet (1784–1845) described such a case [*36*], in the sixty year old Marie Lefèvre and subsequently (in 1840) stated that he had seen three similar cases also at autopsy. On a purely statistical probability, a polyp in the esophagus and stomach is more likely a myoma, while in the colon and rectum it would most probably be an adenofibroma.

A pedunculated, sarcomatous polyp, implanted on a broad stalk, was found in a forty-five year old woman, who had been anatomized in 1802 in Edinburgh by the previously mentioned Monro, II. His son, Alexander Monro, III (1773–1859) included this case in a classic text [*191*]. The description and the wood-

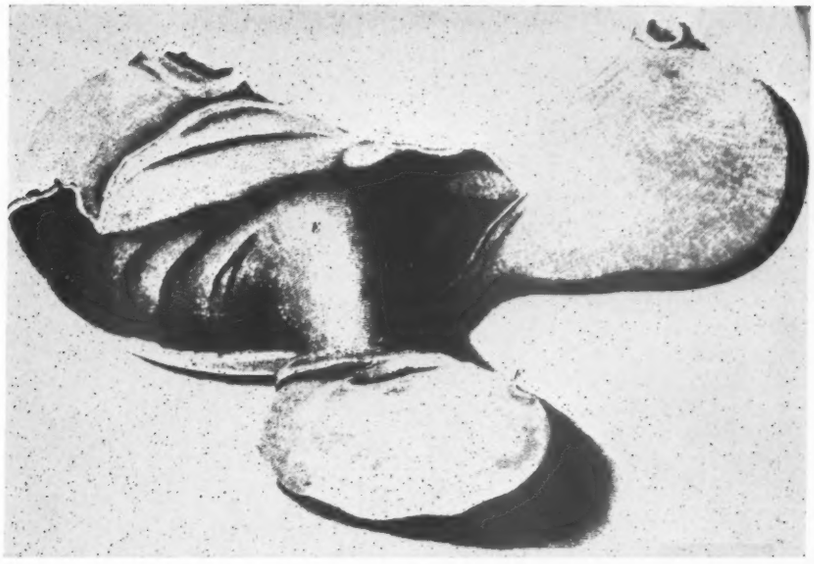

FIG. 8. In the words of Monro, II, (as told to Monro, III [*191*]) the former owner of the stomach pictured in Figure 7 had been a middle-aged woman who "lost her colour, flesh, and strength" until she died emaciated in 1802. At autopsy this smooth-surfaced, firm-bodied polypus was found adhering by a broad-based neck to the posterior gastric wall. It was probably of myomatous nature. (Reproduced through the courtesy of the John Crerar Library, Chicago.)

cut (Fig. 8) leave no doubt about the fact that this had been a myomatous polyp.

In 1826, in London, John Webster (1795–1876) described a calcified antral polyp (firmly attached to the coats of the stomach) which had caused pyloric obstruction (*cf.* [*215*]).

The first intramural gastric myoma was reported by the Italian father of clinical pathology, Giovanni Battista Morgagni (1682–1771). In 1745 he opened the body of a seventy year old woman, who had died of pneumonia, and found a partly calcified, submucous tumor in the posterior gastric wall. He published a report of it in 1762 [*193*] at which time he also described a non-calcified, submucous, prepyloric tumor in the body of a very old man [*193*]. The "enormous" gastric tumor found by Heinrich Bass (1690–1754) in a nonagenarian [*17*] was probably not a myoma.

The previously cited Hunter (Fig. 9) and Baillie's German translator, Samuel Thomas Sömmering (1755–1830) had also seen asymptomatic intramural tumors [*13*]. Johann Gottlieb Walter (1734–1818) collected, and Friedrich August Walter (1764–1826) described the case of a sixty year old woman in whom a white, oval stone was found between the muscular and the "nervous" coats of the stomach [*287*]. The Scottish physiologic surgeon Charles Bell (1774–1842) saw a somewhat similar case [*23*], while John Webster (1795–1876) found a very hard (bony) polyp in the pylorus [*290*].

Of more significance, however, was the almond-sized tumor discovered by Julius Vogel (1814–1880) in the wall of the lesser gastric curvature of a forty-four year old man who had died of renal disease. Vogel made slides of it, and remarked how closely it resembled the uterine fibroid. This observation, published in Leipzig in 1843, was the first histologically authenticated gastric leiomyoma [*281*]. (Fig. 10.)

On July 26, 1858, Charles Eliot Ware (1813–1887) presented to the Boston Medical Society a report on an ulcerated gastric fibroid [*288*]. Before the same society, the pioneer New England pathologist John Bernard Swett Jackson [*122*] (1806–1879) exhibited an hourglass tumor of the stomach, forwarded by a physician from Fichburg, named Hitchcock. On this occasion, Jackson emphasized the strange macroscopic and microscopic resemblance between this dumbbell tumor and six small tumors found in 1861 in the stomach of a tiger (suffocated in a menagerie fire) [*133*]. Leiomyomas are encountered in many animals, for instance in the stomach of the horse [*106,162*].

SMALL INTESTINE

The most obvious danger from these tumors, in Monro's words [*191*], is that they "create

FIG. 9. The original caption, prepared by Baillie [*14*] for this woodcut of 1799 and executed after an anatomic preparation preserved in the museum of William Hunter, specified that the parts of the stomach in the vicinity of the tumor were "quite sound in their structure. A, inner surface of stomach at its smaller end, free from disease; B, ridge of pylorus; C, small portion of duodenum in healthy state; D, circumscribed tumour, covered by inner membrane of stomach. In its center is a small aperture; E, section of tumour to illustrate its structure. It consists of a whitish substance, having a gristly hardness, and in some parts is slightly intersected by the membrane." It was a calcified and ulcerated submucous gastric tumor (most likely of smooth muscle origin !). (Reproduced through the courtesy of the John Crerar Library, Chicago.)

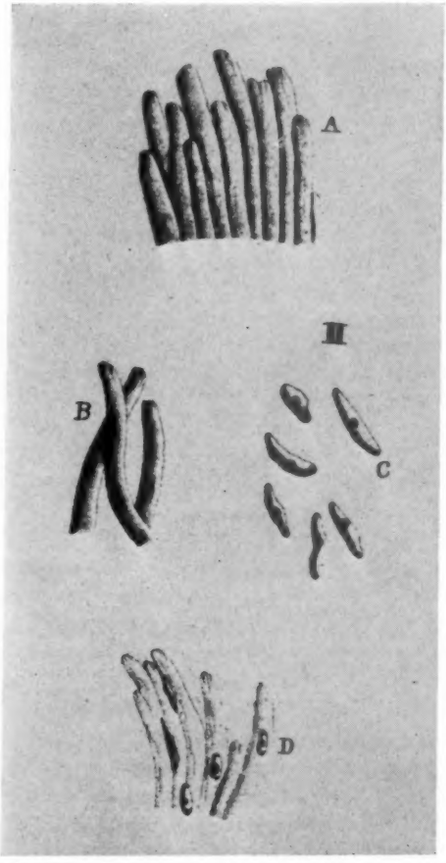

FIG. 10. This drawing (*tabula* VII, Fig. 2) [*281*] was made by Vogel himself and published in 1843. It is the low power, microscopic appearance of an asymptomatic gastric leiomyoma (the *first* histologically authenticated), found during autopsy of a male patient who had died of renal disease. Vogel remarked how closely its structure resembled that of uterine fibroid, which in the original publication was pictured on the same table (*tabula* VII, Fig. 3) [*281*]. (Reproduced through the courtesy of the John Crerar Library, Chicago.)

colicky pains by obstructing the Intestines, and impeding the progress of the faeces."

A forty year old woman (from Albany, New York) died in 1828 of intestinal occlusion. The distal jejunum was obstructed by a "firm, fleshy, semi-cartilaginous tumor . . . arising from the muscular and covered by the mucous coat, entirely filling the gut." E. A. Leonard, a local practitioner, composed this meticulous, autoptic description [*151*].

By contrast, the intramural tumor found by Johann Leberecht Schmucker (1712–1786) had caused no symptoms [*247*]. The sixty-five year old man, examined by Thomas Bevill Peacock (1812–1882), had died because of "internal strangulation" resulting from the presence of a "fibrous polyp" [*212*]. A classic text on these *étranglements internes* was the 1859 Paris Academy of Medicine prize essay written by the surgeon Auguste Philibert Duchaussoy (1827–1918): among the various conditions which may precipitate an intestinal stranglehold was included the "simple hypertrophy of the muscular coat of the intestine" [*66*].

COLON

The earliest recorded observation in this category was published in 1741 by the Dutch surgeon, playwright and epidemiologist Nicolaas Fonteyn. The patient, a seventy-eight year old man, died of "disentery" while the autopsy brought forth in the colon a pedunculated polyp, 8 inches long, weighing 1 pound [*88*]. (Fig. 11.)

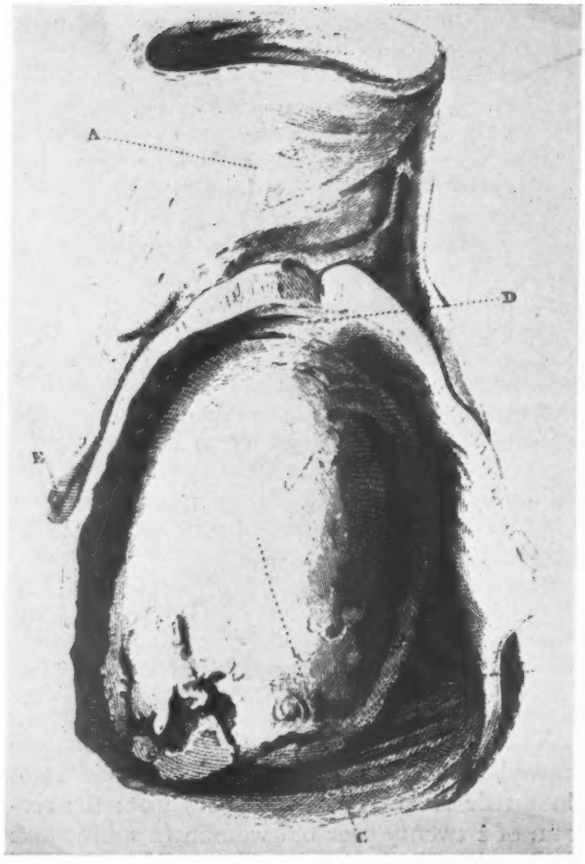

FIG. 11. In Baillie's own words, this woodcut of 1800 executed after an anatomic specimen from his collection, represents "a considerable polypus which had grown in the sigmoid flexure of the colon, forming a cause of obstruction which is very uncommon. A, part of the colon in sound state; B, part of the colon laid open, in order to bring the polypus into view; C, the polypus; D, neck of the polypus (the coats of the colon are thickened near the neck of the polypus); E, one of the appendiculae epiploicae" [*14*]. A myomatous colonic polyp would look like the one pictured. On a simple, statistical basis, however, a polyp in the colon is adenomatous until proved otherwise (while in the esophagus and stomach it is myomatous, unless histologically excluded). (Reproduced through the courtesy of the John Crerar Library, Chicago.)

Four other instances of colonic obstruction shall be herein mentioned. More compatible with a retrospective diagnosis of smooth muscle tumor is the case of a sixty-six year old provincial functionary from Coutras (near Bordeaux), who died in December 1757 of "incurable constipation." The autopsy, performed by Leboeuf, revealed a fleshy excrescence which occluded the sigmoid [*149*]. The other three cases [*155,214,300*] occurred in children. They are cited in this context by other authors, but their smooth muscle origin is somewhat doubtful.

There are on record instances of *iliac passion*

FIG. 12. Alvine elimination of this polyp (which occurred in 1758) terminated the *iliac passion* (obstructive ileus) of a young housewife. Meckel, who reported this case history [*180*], assumed that the polyp had been lodged in the splenic flexure (a mass in the left upper quadrant disappeared as the polyp was eliminated). The myomatous nature of this polyp may be suspected because of its (apparent) twin roots; they are the result of basilar cystic degeneration, which in this form is rare in adenomas. (Reproduced through the courtesy of the John Crerar Library, Chicago.)

(time-honored, but today obsolete term for ileus) which receded after spontaneous elimination of (part of) a tumor *via* the natural exit.

The observation-princeps is from the pen of Johannes Gottlieb Bauer (1698–?), who had graduated in 1724 in Halle with a thesis on polypus of the heart. In a letter to Johann Gottfried von Hahn, dated 1747 in Dresden, Bauer related how the intestinal obstruction of a forty-eight year old man was suddenly "cured" after defecation of a "fibrous and fleshy concretion." The "concretion" was promptly labeled an "intestinal mole" [*19*], since *mola* was the neo-Latin term for the Hippocratic uterine polyp [*99*].

In the summer of 1758 Johann Friedrich Meckel (1724–1774) examined a thirty year old woman who had a mass in the upper left quadrant. After seven days of cramping and bloating the patient eliminated a twin-rooted polyp (Fig. 12) which, from its size and shape, was assumed to have originated in the splenic flexure. There was little bleeding, and the patient regained her previous health [*180*].

Robert Archer (1794–1877) of Philadelphia reported a similar "cure" following the evacuation "per anum" of a "sarco-steatomatous" tumor from the

distended bowels of a plethoric, fifty year old woman [*11*]. Fee described an identical occurrence in a ten year old girl from Leatherwood (Indiana). Her ileus was instantaneously relieved in September 1845 after passage of a "partridge egg-sized polypus." The unlucky Fee did not see the offender: the polypus, left nonchalantly on the ground (where it had "fallen") was "swallowed by the poultry" [*81*].

The first microscopic examination of tissues eliminated in this manner was reported in 1874 by an art anatomist and pathologist from Florence (Italy): Giorgio Pellizzari (1814–1894) saw a young girl in whom the intestinal obstruction and mass in the lower right quadrant disappeared after elimination of a rounded tumor weighing 500 gm. He examined the tumor, which was very soft, and it turned out to be a pure myoma [*213*].

In April 1851, Amédée Deville (?–1879) displayed before the Société Anatomique of Paris "foreign bodies" found in the peritoneal cavity. Verneuil examined them, and decided they were fragments from a "fibroma" [*64*] (presumably from an extraluminal smooth muscle tumor because, since Bayle, this was the term used for uterine myomas !).

There is, of course, quite a difference between spontaneous and forcible detachment. In 1836, Edouard Meulewaeter (1810–1873), who later became a respectable professor of medicine in the University of Gand (Belgium), took care of a twenty-eight year old man, named Zwartelée. For years the latter had had a "rectal" polyp which finally appeared at the anus. With a surgeon in attendance, Meulewaeter grasped the polyp, and "pulled" it out. The polyp weighed 5 ounces, it was fibrous in appearance, and its lengthy pedicle seemed rooted in the muscularis. Unfortunately, the patient died of peritonitis. Autopsy showed a perforation at the site of the polyp's insertion near the junction of the sigmoid and descending segments of the colon [*186*].

RECTUM

The earliest known mention of what may have been a smooth muscle tumor of the rectum can be found in a 1728 publication of the famous Dutch iatrochemist Hermann Boerhaave (1688–1738). The patient, a man from Amsterdam, suffered of tenesmus caused by thickening of the fleshy (muscular ?) layers of the rectal wall [*30*].

Very detailed is the case report prepared by Marcus Elieser Bloch (1723–1799), a Jewish surgeon from Berlin, whose patient, a thirty-six year old male tailor, suffered from "constipation" from January 5 through February 16, 1768. For a while Bloch succeeded in maintaining the patient's rectal patency by using a candle as a dilator. Autopsy revealed a heavily anchored rectal polyp, which resembled the "true polypi found in the uterus" [*29*].

A German practitioner, Carl August Tott (1795–1856) reported cessation of rectal bleeding in several children following ligature and removal (in each case) of a *sarcoma polyposum in ano* [*274*]. These were hardly leiomyomas, but the terminology must have been very enticing: it was still used occasionally in twentieth century Montpellier (France) [*176*].

Although the Hippocratic writers described five types of polypi, these could all be reduced to two types: soft (fleshy or sarcomatous) and hard (fibrous). In the 1830's, a Franco-German gynecologist from Strassbourg, Joseph Alexis Stoltz (1803–1896), suggested a more detailed classification. Thereafter several categories were described [*99*], and in 1853 the Paris surgeon Amédée Forget (1811–1869) classified rectal polypi into mucous, fleshy, cystic and fibrous, and added a fifth category (with reference to Bayle [*21*]): *corps fibreux* [*89*].

There is no doubt that the *corps fibreux*, removed successfully in 1843 by Antoine Joseph Jobert de Lamballe (1799–1867) from the rectum of a twenty year old woman (a submucous tumor, smooth, oval, bleeding) was a leiomyoma. The report [*90*], prepared by Forget, is somewhat ambiguous as to whether or not the specimen was examined microscopically (probably not!).

The first record of histologically authenticated rectal leiomyoma is dated 1872. The surgical pathologist Aristide Auguste Stanislas Verneuil (1823–1895) had shown (to the same Société Anatomique in Paris) a "fibroma of the rectal mucosa" diagnosed macroscopically. Thereupon, Louis Charles Malassez (1842–1909) mentioned *en passant* that one of the rectal polypi seen by him exhibited the structure of a fibromyoma [*278*]. The first detailed descriptions of rectal myoma were published in 1881 [*41,217*].

MEDICOHISTORIC PHASES OF LEIOMYOMA

At whatever date in the history of medicine it may have been "conceived," leiomyoma was "delivered," for all practical purposes, by Virchow in or about 1860. As it was "growing up," leiomyoma followed a pattern encountered quite often in the nosology of internal medicine.

At first, the "alimentary" smooth muscle neoplasia remained in its *pathologic* phase. For decades, tumors of "unstriped muscular fibre"

[*59*] were found almost exclusively at autopsy. Since most pathologists were unfamiliar with the lesion, it often went unrecognized. The situation was such as to justify in 1870 a paper describing a polypous myoma of the ileum, based on an anatomic preparation from the year 1844 [*33*].

Its *surgical* phase dawned in the 1890's, when surgeons began to find, identify and excise (cure?) the condition. This led, sooner or later (depending on localization), to the collection of series of case reports, proving that these tumors were not as rare as previously believed.

Finally, after another three decades, i.e., in the 1920's, the *clinical* phase was approached. This is when internists (with the help of roentgen, endoscopic and laboratory findings) learned to suspect preoperatively, or at least antemortem, the existence of such tumors in the walls of the digestive tract.

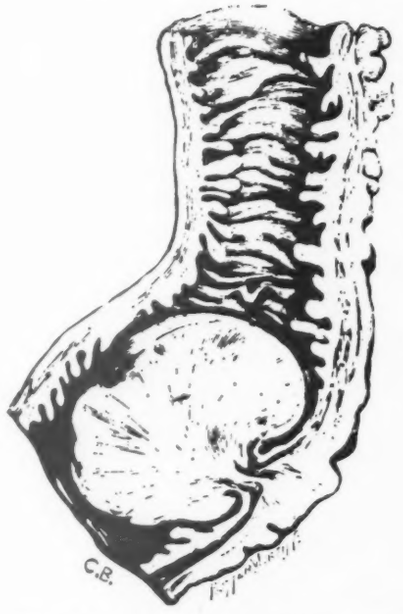

FIG. 13. Bland-Sutton called "sarcomatous fibroid" those uterine polyps which resembled spindle cell sarcomas. As he had uncovered a very similar histologic structure in this polypous fibroid (found in the small intestine) he proposed to give it the same name [*27*]. In contradistinction to Shakespeare's eternally sweet-smelling rose, confusing nomenclature should be banned from scientific publications. (Reproduced through the courtesy of the John Crerar Library, Chicago).

MALIGNANT SMOOTH MUSCLE TUMORS

The controversy over the malignant variants of smooth muscle neoplasia started during its pathologic phase. Virchow had used the term *myosarcoma* (even the mythical *myocarcinoma* [*280*]), but the problem itself was first raised by the Polish pathologist Ludomir Wlodzimirz Brodowski (1825–1903). In 1876 he described a giant, exogastric myo(fibro)sarcoma which had killed a fifty-seven year old man. The strange thing about it was that the liver metastases consisted of pure myomatous (not myosarcomatous) tissue [*38*].

The denomination *myoma sarcomatodes* was applied in 1872 to a tumor of the (right) kidney [*68*] by Carl Johann Eberth (1835–1911) who, at the time, was a pathologist in Zürich. He is remembered today not only for his studies on "cretinism in the calf" but also for the description of a giant esophageal myoma found in the body of a fifty year old tuberculous psychotic woman [*67*].

In Trieste, the experimental oncologist Benedetto Morpurgo (1861–?) performed an autopsy on a fifty-four year old woman. He found a submucous intestinal myoma with noticeable metaplasia and tendency to local invasiveness. At the same time her uterus contained several myomatous nodules with cellular elements resembling the transitional stages toward the (characteristically) spindle-celled sarcoma. In 1895 Morpurgo called the uterine lesion *myoma sarcomatodes*, but for the intestinal tumor he coined the name *leiomyoma malignum* [*195*]. The distinction went beyond a subtle linguistic *leger-de-main*. Malignant leiomyoma was supposed to have malignant characteristics from its very inception. Myoma sarcomatodes would start out as a benign tumor, which subsequently was to degenerate into a malignancy. With a similar purpose in mind, in 1898 Rudolf Steiner (then of Prague) used the term myosarcoma for the malignancy *ab-initio*, and reserved the name *myoma sarcomatosum* for the "degenerated" type [*262*]. (Fig. 13.) The now consecrated contraction *leiomyosarcoma*, used in 1908 by the Vienna surgeon Viktor von Hacker [*109*] (1852–1933), became popular in this country in the 1930's [*8*]. Even so, the "old-timer" myosarcoma is not obsolete, not yet, anyhow!

All subsequent arguments are mere amplifications of these earlier endeavors, particularly with regard to nomenclature, from myoma sarcomatodes [*71*], to malignant (leio)myoma [*15,22,223,224,238,251*]. Until World War II the latter terminology (and concept) were favored by the majority, including the Vienna tuberculopathologist Anton Ghon [*101*] (1866–1936).

Every so often somebody would reiterate that "benign" smooth muscle tumors can and do metastasize [*63,114,156,183*], and there would be debates to determine whether leiomyosarcomas are malignant from their very beginning [*169,170*] or whether they are originally benign and degenerate afterwards [*12,146,223*]. The problem may have certain surgical undertones, as it could imply the need to search

for asymptomatic (benign) lesions, and to resect them before they have time to degenerate.

In the view of Hans Hufnagel (of Heidelberg), his *myoblastic sarcoma* [*126*], which is just another fancy name for leiomyosarcoma, was an example of "ultra-differentiated myosarcoma." His intention was to emphasize that the biologic potential of smooth muscle tumors defeats any morphologic recognition (cytologic unpredictability). In this respect the surgical oncopathologist Lauren Ackerman [*3*] (of St. Louis), and the internist Peter Masley [*175*] (of New York) agree that, not infrequently, leiomyomas are histologically benign, but clinically malignant.

Fortunately for the positivistic approach in clinical pathology, John Berg and Gordon McNeer [*24*] have restored faith in histoclinical correlation. In their twenty-four cases of gastric leiomyosarcoma (seen between 1935 and 1955 at the Memorial Center for Cancer in New York), there had been a strict concordance between anaplasia and malignant outcome, and their entire series of four tumors (with this feature) recurred after surgery.

Unfortunately, most other pathologists continue to have occasional difficulties in deciding whether a given case of smooth muscle tumor is benign or malignant [*259*]. Excessive cellularity of certain benign lesions may be a cause of confusion with sarcoma. The association of pleomorphism and atypical mitoses must nonetheless be regarded at least as a presumptive sign of malignancy [*102,104*].

And yet, when the chips are down, one may find himself in the predicament of the Canadian Air Force surgeon Wilfred Noble Coombes (of Ottawa), who had to decide whether to write out a duodenal smooth muscle tumor as malignant or benign. He favored the latter, but then leaned toward the former [*56*]. In some of these Janus-faced neoplasms, if one refuses to toss a coin for or against malignancy, the only alternative is to wait, and have almighty Time make the final decision. Apparently, the malignant potential is enclosed (hidden ?) within these neoplasms, which justifies, in the title of the present review, the parenthetically intratwined contraction leiomyo(sarco)ma.

METASTASES

Julius Friedrich Cohnheim (1839–1884) regarded the degree of malignancy of a tumor to be a matter determined by the host's response [*54*]. This view holds the promise that some day ways may be found to influence (favorably) the body's reaction to oncologic aggression.

Histologically "bad-looking" smooth muscle tumors may never metastasize, and vice versa. Metastases are generally considered *prima-facie* evidence of malignancy, but in leiomyosarcomas their presence does not necessarily imply death on short notice [*227*].

In the case reported by Rudolf Demel (of Vienna), two years elapsed between the surgical discovery of a "primary" liver myoma, and the autoptic demonstration of its jejunal origin [*63*]. One wonders whether Elmar Stöcker (of Gelsenkirchen, Germany) did not overlook a gastrointestinal primary leiomyo(sarco)ma in his investigation of a generalized malignant leiomyomatosis (with foci everywhere, including lungs, myocardium and kidneys). It was histologically so benign that he labeled it *hamartoblastomatosis* [*264*]!

As a group, smooth muscle tumors of the alimentary tract metastasize infrequently. When they do, it is mostly to the liver [*175*], occasionally to regional lymph nodes, seldom to the peritoneum [*102*]. Although blood-borne, metastases very rarely transgress the confines of the abdomen. They have been encountered in the lungs [*181*]. Theoretically, they could reach any organ.

There are in the literature observations establishing the concomitant presence of leiomyo(sarco)mas in the esophagus and uterus [*205*], in the stomach and uterus [*172,224*], in the gastrointestinal canal and skin [*271*], in the appendix and uterus [*15*], even in succession in the uterus and duodenum [*257*]. Still, none of these authors (or Morpurgo [*195*] before them) ever considered seriously a metastatic relationship between such coincident localizations.

"FIRST" MALIGNANT CASE REPORTS

It is reasonable to assume that some of the "(pre)historic" cases of smooth muscle tumors of the alimentary tract must have been malignant. Evidently, histologic proof of their malignancy could not be expected until after 1830, the posthumous date of appearance of a tract [*124*] by Everard Home (1756–1825) which was the first publication containing microscopic illustration of tumor tissue.

In the *stomach*, the first report of a malignant

smooth muscle tumor was published in 1847 by the (subsequently psychotic) anatomophysiologist Carl Wilhelm Ludwig Bruch (1819–1884). He had found a fungating tumor (*Markschwamm*) on the posterior gastric wall of a forty-six year old dyspeptic man, with lymph node metastases and spindle cells on the microscopic slides [*40*].

In the *rectum*, the first such case was shown to the Boston Medical Society on December 12, 1859. The patient had been treated for bloody diarrhea since November 1857 by the Harvard professor of materia medica, Edward Hammond Clarke (1820–1877). He then referred her to the professor of internal medicine, Calvin Ellis (1826–1883). In October 1857 (two months before her death), the patient eliminated per rectum a rounded piece of tumor. Autopsy revealed a polypoid, fungating, dumbbell type of lesion (located 6 inches from the anus), consisting of granular, elongated, fusiform cells, with noticeable "nuclear changes"* [*74*].

In the *esophagus*, the first malignant smooth muscle tumor was reported in 1877 by Sherman Hartwell Chapman (1847?–1903), a Columbia graduate of 1869, who practiced in New Haven, Connecticut. His forty-five year old female patient starved to death. Chapman noted judiciously that she had had an "innocent sarcoma, the death (having been) produced by the accident of its situation (rather) than from the violence of its constitutional effect" [*50*].

The other three "firsts" were found by surgeons. The first myosarcoma in the small intestine (probably *ileum*) was described in 1897 by the Roumanian pathoparasitologist Victor Babes (1854–1926). The tumor had been resected from a thirty year old man by the surgeon George Nanu (in Filantropia Hospital, Bucharest) [*12*]. Anton Wölfler, in Prague, excised a giant (7 kg.) external myosarcoma of the *jejunum* from a fifty-seven year old woman. The report was printed in 1898 by Steiner [*262*]. In the *duodenum*, the first recorded myosarcoma occurred in a forty year old man. The patient underwent an exploratory examination by Fritz de Quervain in Berne, in July 1918, and an autopsy by Karl Wegelin four months later; the case was reported in 1920 by Hans von Salis [*236*].

* The *Blutschwamm* removed by Schlesier on June 15, 1843, from the rectum of a fifty-two year old giant man was probably a myosarcoma, but the histology was missing [*243*]. Similarly incomplete is Laracine's earlier report [*147*].

TRANSITION FROM PATHOLOGIC TO SURGICAL PHASE

Intestinal leiomyo(sarco)mas were the earliest conquered. The old French master Auguste Nélaton (1807–1873) performed the first laparotomy on such a patient sometime before 1882 [*202*]. The first successful resection, accomplished in 1884, is credited to Alfred Heurtaux [*118*] of Nantes (France). A similar success, registered in 1885 by Vincenz Czerny (1842–1916), was reported by the German gastroenterologist Wilhelm Fleiner [*87*] (1857–1926). Except for unexpected (associated) situations, peculiar to a given case, the procedure seldom presents special problems. Indeed, surgery may be "life saving" when bleeding [*47*] or obstruction exist. Excision has been "curative" in a two year old child in Tanganyka [*143*], as well as in a newborn [*37*].

Case reports of smooth muscle tumors in the wall of the rectum have always been scarce [*186,225,271*]. The first resection of a "subserous myofibroma" of the rectum [*253*] was performed in 1890 in Milwaukee by the military surgeon and clinical oncologist Nicholas Senn (1844–1908).

Similarly successful operations were reported in 1896 from Stockholm by Frans Johan Eugéne Westermark [*295*] (1853–1941), in 1897 from Breslau by Hermann Johann Pfannenstiel [*216*] (1862–1909), and in 1898 from London by Thomas Carwardine [*46*] (?–1947). The last three were gynecologic surgeons, and the patients, including Senn's, but excluding Carwardine's (a forty-one year old male miner), were women.

Gastric leiomyoma was first attacked surgically in 1890 by Rudolf Kunze (in Dresden). The subserous tumor was easily resected, but the fifty-two year old male patient died fifteen days later of pneumonia [*144*]. The first successful removal of exogastric myoma was reported in 1895 by Hermann von Erlach [*75*], of exogastric leiomyosarcoma in 1897 by Anton von Eiselsberg (1860–1939), both of Vienna. Other pioneers are listed in one of the first surgical reviews [*196*]. Long before the 1930's surgeons all over the world [*84,210*] had become quite proficient in the technical details involved.

Because of the mediastinal location, esophageal smooth muscle tumors constituted a long-standing frontier.

Often cited specific cases of such tumors found at autopsy were communicated from Glasgow by Joseph

FIG. 14. This huge, intramural (histologically proved) esophageal leiomyoma was found in 1874 by Charles Hilton Fagge (1838–1883) during the autopsy of a thirty-eight year old male patient who had died in Guy's Hospital of severe pulmonary emphysema (cor pulmonale ?). Careful retrospective inquiry failed to reveal any symptomatology referable to the esophageal tumor. This, in Fagge's opinion [*78*], casts serious doubts on the often voiced assumption that hypertrophic lipping of the cervical spine might cause dysphagia by extrinsic pressure on the esophagus. (Reproduced through the courtesy of the Medical Library of the University of Illinois, Chicago.)

Coats [*53*] (1846–1899), from London (Fig. 14) by Charles Hilton Fagge [*78*] (1838–1883), from Nantes by Etienne Trastour [*275*] (1828–1896], from Cleveland by William Travis Howard, Jr. [*125*] (1867–1918?), and from Vienna by Alfred Exner [*76*] (1874–1921).

In 1932, from Berlin, the celebrated thoracic surgeon Ferdinand Sauerbruch (1875–1951) reported the first successful extirpation of an esophageal myoma [*237*], one year before the Japanese Ohsawa recorded the second such case [*204*]. During World War II chest surgery made notable advances, and today partial esophagectomy is a standardized procedure [*209*].

ROENTGEN HISTORY OF LEIOMYO(SARCO)MA

The first recorded use of barium meal in "alimentary" smooth muscle tumors is dated 1911. The Paris radiologist Gaston Raulot-Lapointe examined a patient who had ingested bismuth paste fluoroscopically and found (and sketched) a filling defect on the lesser gastric curvature, whereupon the surgeon Antonin Gosset removed what proved to be a myosarcoma [*106*].

In 1914, in Berlin, Max Schiller examined a patient with an epigastric mass fluoroscopically, and observed extrinsic pressure on the lesser curvature; the autopsy showed a gastric myosarcoma [*240*]. In 1916, in Vienna, the internist Hermann Schlesinger mentioned that a tentative (subsequently confirmed) diagnosis of gastric lymphosarcoma had been made by the roentgenologist Joseph Freud (one of Holzknecht's pupils), and thought this should soon be possible with leiomyo(sarco)mas [*244*]. In 1917, in Basel, Emanuel Geymüller published the first report [*100*] on roentgenologic examination in gastric sarcoma. His case report was that of a forty year old woman from whom de Quervain had successfully removed a submucous fibro(myo)sarcoma.

The first preoperative diagnosis of gastric fibromyoma was claimed in 1921 by Viktor Lieblein (1869–1938), a surgeon from Prague [*154*]. Roentgenologic-anatomic correlation studies were required before results could become more than fortuitous. In 1921 the roentgenologist of the Mayo Clinic, Russell Daniel Carman (1875–1926), described his eponymic (semilunar halo) sign [*42*] in malignant gastric ulcer. Together with rigidity and raggedness it was merely a translation into negative shadows of the infiltration of invading neoplasm.* Its reverse, the soft, pliable, well defined, localized, i.e., "benign" appearance was found when the contemporary German roentgenologist Heinz Lossen indicated, in 1922, preoperatively a benign tumor in what proved to be an antral fibromyoma [*161*].

At this point, special mention must be made of the classic paper [*192*] on the roentgenologic features of benign gastric tumors written by one of Carman's associates, Alexander Berkeley

* In 1917 Carman had described the roentgenologic examination of a sixty-five year old woman who had a palpable tumor in the left epigastrium. Her "very unusual filling defect" involved the distal half of the stomach, and this was interpreted as inoperable carcinoma, but the surgeons "exsected" an orange-sized, prepyloric fibromyoma which had invaginated through the pylorus into the duodenum [*43*].

Moore (1883–1946), who later practised roentgenology in Washington, D. C. The first paper specifically devoted to the roentgenologic features of gastric myoma was published by Hans Gebhardt [*98*] (of Prenzlau, Germany) in 1930. Since most smooth muscle tumors are histologically "benign," more often than not their roentgenologic features are correspondingly "innocent," as noticed also by the tuberculo-roentgenologist and historian Samuel Aronovich Reynberg [*288a*] (of Moscow).

The roentgenologic findings of intestinal smooth muscle tumors resemble those of lymphosarcoma. The basic article [*94*] on the subject was published in 1916 by the previously mentioned Joseph Freud (1882–1925), remembered also because he died of radiation damage after he had migrated from Vienna to Jerusalem and had become the roentgenologist of Hadassah Hospital. To this may be added the now almost forgotten description of the "vacuole" (filling defect) in the duodenum, contributed by Ross Golden [*103*] (who at the time was the roentgenologist of Presbyterian Hospital in New York). The appearance of the extraluminal form of duodenal leiomyosarcoma was described by Brdiczka [*35*] (of Berlin).

One must advance to the 1940's before finding in the literature roentgenologic reports of smooth muscle tumors in the colon [*105*] or esophagus [*115,239*]. With regard to the colon, this is explained by the penury of cases. In the esophagus, leiomyo(sarco)mas acquired notoriety, and thus the need for roentgenologic identification, only after the surgical conquest of the mediastinum.

FREQUENCY

Figures available in the literature are heavily biased by the respective pathologist's (un)willingness to be(come) aware of the existence of leiomyo(sarco)mas. Until World War I, in some areas even after World War II, "alimentary" smooth muscle tumors were considered rare curiosities.

In 1898 Steiner collected from the literature the reports of a total of fifty-seven cases (twenty-one in the stomach, the others distal to the pylorus) [*262*]. In 1912 Martin Hake added sixty cases (thirty-six of which were in the stomach) [*110*]. (Thereafter tabulations were made by organs.) In 1913 a review appeared with eighty-four cases of gastric myomas [*80*]. There were 140 such cases in 1915 [*199*], and 321 in 1926 [*72*], but one year later more stringent criteria were applied and the total figure dropped to 211 [*203*]. In 1932 it was back to 319 [*183*], and in 1938 it had climbed to 539 [*55*], but a few months later it was down to 338 [*49*]. In 1951 it jumped to 610 benign cases, perhaps because the military pathologist Eddy Davis Palmer had compiled his (both thorough and excellent) monograph [*208*] with the help of what was then called the Army Medical Library (it is today the National Library of Medicine). In 1960 a collective review was published, up to 1958: 1,017 gastric smooth muscle tumors had been found of which 704 were benign, 201 were malignant (as compared with 94 leiomyosarcomas, tabulated [*241*] in 1946), and five borderline [*259*]. In the meantime, in 1953, one author published a condensation of fifty personal cases of gastric myomas [*9*] (but all these figures seemed to constitute no deterrent to the publication in 1959 of another *single* case report [*177*])!

From the pylorus downstream, the incidence of myomas decreases to a comparative trickle. In 1933, in the Mayo Clinic material, Fred Wharton Rankin found only six duodenal myomas [*226*]. In 1952, only fifteen case reports were collected from the universal literature [*267*]. In 1953, another paper assembled the records of twenty-eight duodenal leiomyosarcomas [*291*], more than the twenty-three cases counted in 1955 [*171*], superseded in 1960 by a review of sixty-one such cases [*261*].

In 1957, sixty instances of jejunal leiomyosarcoma were counted in the literature [*227*]. Until 1955, a total of twenty-seven benign and ten malignant myomas in the colon had been reported in the literature [*179*].

Cases of rectal myomas are fewer yet, and some of these have been listed together with non-myomatous rectal sarcomas [*277*]. The first (seldom if ever quoted) review on the subject was published in 1908 by the Polish surgeon Tadeusz Ostrowski [*207*] (1881–1941), the second in 1921 by Verne Carlton Hunt [*128*] (1888–1943), who at the time was in the Mayo Clinic, but later settled in Los Angeles. By 1955, twenty cases of rectal leiomyosarcoma could be numbered [*206*].

The first collected series of esophageal myomas [*189*], limited to its polypoid variety, was published in 1895 by Peter Romuald Minski (1864–?) of Tartu (Estonia). In 1950 a review of ninety-two cases appeared, of which eight patients had been operated upon, and six had survived [*61*]. In 1954 the total number of esophageal myomas reached 155 (108 found at autopsy, forty-seven at surgery) [*153*]. In 1956 the total had increased to 236 cases [*265*]. In 1958 twenty case reports of esophageal leiomyosarcomas had been collected [*173*].

To these may be added, in the guise of real curiosities, six cases of smooth muscle tumors in the mouth [*266*], and two in the pharynx [*65,255*].

The total number of case reports of esophagogastrointestinal leiomyo(sarco)mas printed to

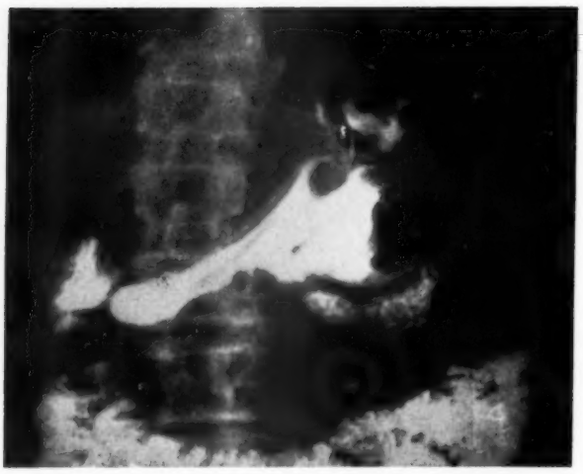

FIG. 15. Perhaps the most important thing to remember about smooth muscle tumors is the fact that (whether "benign" or "malignant") they are often still resectable, and "curable" at a stage of development at which a carcinoma, of comparable size and extensiveness, is almost certainly inoperable. This roentgenogram is from a fifty-six year old man, prior to removal (in Cook County Hospital, on February 24, 1956) of a gastric leiomyosarcoma. The patient was still alive and well, three years after surgery. (Reproduced through the courtesy of Dr. Paul Nora.)

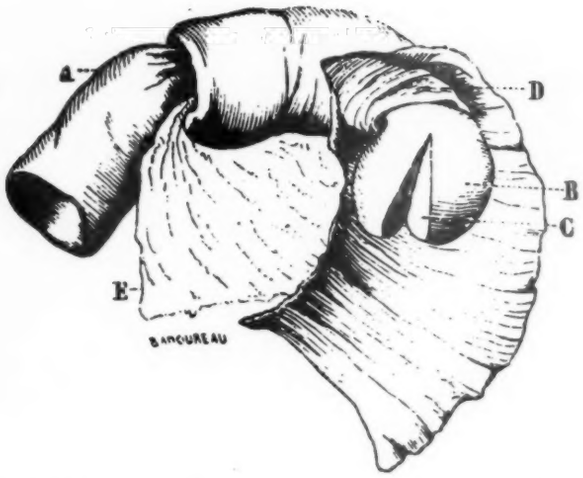

FIG. 16. This drawing, reproduced from a French surgical textbook [*202*], was made after an English anatomic specimen (Hunter's museum, nr. 1378). It shows intestinal obstruction (site not specified), due to "invagination" of a "muscular" polyp, with resultant triple-layered, concentric cylinders. The modern term is intussusception. (Reproduced through the courtesy of the Library of the University of Illinois, Urbana.)

this day in the universal literature can be estimated conservatively at 2,000. It is more likely closer to 2,500. The condition is not rare, except for choice locations, such as mouth, rectum and colon.

Available figures for the relative frequency of "alimentary" leiomyo(sarco)mas are also too uncertain to be used as a baseline. The *gastric* localization is, beyond any doubt, the most often encountered (about 3:1 over all other sites combined). The *esophageal* is next in line, with the *cardioesophageal* [*148,249*] as the third (provided such cases are listed separately from both stomach and esophagus). Way down on the list are the small intestine (jejunum, duodenum, ileum), then the other locations.

TREATMENT

Resection is the only logical therapy for symptomatic leiomyo(sarco)mas in the alimentary tract. Radiation is useless [*206*], presumably because of the high degree of differentiation, reports to the contrary [*270*] notwithstanding.

In these tumors neither local spread, nor "malignant" histologic appearance, not even distant metastases, are definite surgical contraindications. Lasting results have been obtained under quite adverse initial circumstances [*169*], sometimes when the roentgenologic appearance suggested an inoperable stage [*58*]. (Fig. 15.) In one instance of esophageal leiomyosarcoma resection was beneficial despite the presence of local extension [*173*].

DIAGNOSIS

Because resection of symptomatic leiomyo(sarco)mas is so often "curative," their detection seems very desirable. And yet there is, so far, only one way to make a positive diagnosis of tumor: histologic examination of a tissue fragment. It remains to determine on what grounds the internist will be justified to demand a biopsy specimen, either by means of endoscopy or exploratory surgery.

SYMPTOMATOLOGIC STUDY

The size, shape and location of "digestive" myomas will determine the extent of disturbance from physiologic conditions.

Extraluminal types will give pressure phenomena only after they reach a certain size (depending on anatomic situation). The intraluminal types cause partial, and eventually complete, obstruction. (Figs. 16 and 17.) Volvulus is another dreaded cause of mechanical ileus. (Fig. 18.) There are innumerable (kaleidoscopic) clinical syndromes under which smooth muscle tumors of the alimentary tract may appear, especially when perforation and other com-

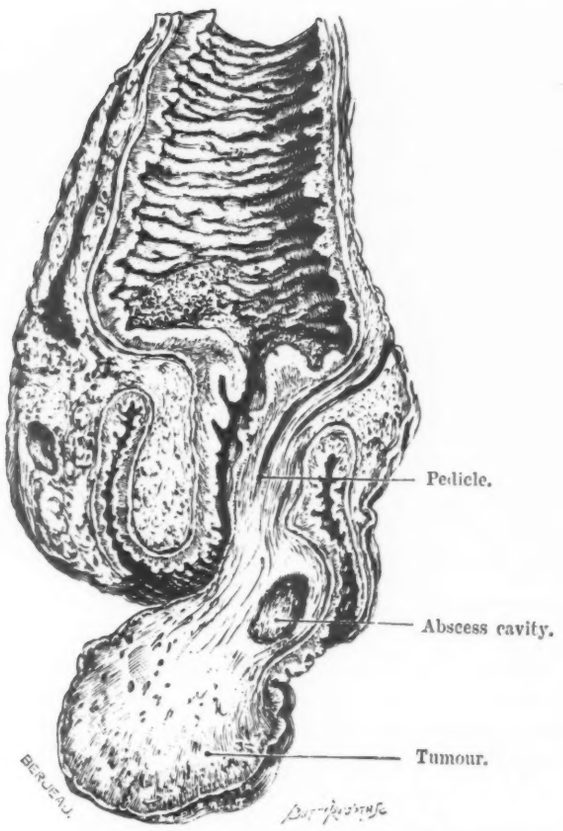

FIG. 17. The three cylinders (*cf.*, caption of Figure 16) can be identified in this segment of jejunum. Bland-Sutton's caption said: "A fibroid had invaginated the bowel and produced fatal intestinal obstruction. From a man aged thirty-five" [*27*]. (Reproduced through the courtesy of the John Crerar Library, Chicago.)

plications are considered. Still, every so often, their identification by strictly clinical means has been investigated, in 1898 in Prague [*262*], in 1923 in Boston [*127*], in 1959 in Aberdeen [*39*].

Gastrointestinal *bleeding* is more often encountered in these tumors than any other single symptom. It leads to microcytic, hyperchromic anemia, which may be severe. As a matter of fact, noticeable (but not occult) bleeding from the intestinal tract, when prolonged or repeated, *in the absence of any other corroborative evidence*, is considered sufficient justification for exploratory laparotomy.*

* Gordon Harvey Sprague, a surgeon from Paris, Illinois, performed an exploratory operation on the abdomen of a sixty-five year old patient (who was the father of another physician) because of recurrent melena; he removed successfully a jejunal leiomyoma. The preoperative small bowel studies did not disclose any evidence of pathology, not even when viewed in the critical light of the *retrospectroscope* (of Leo Riegler.)!

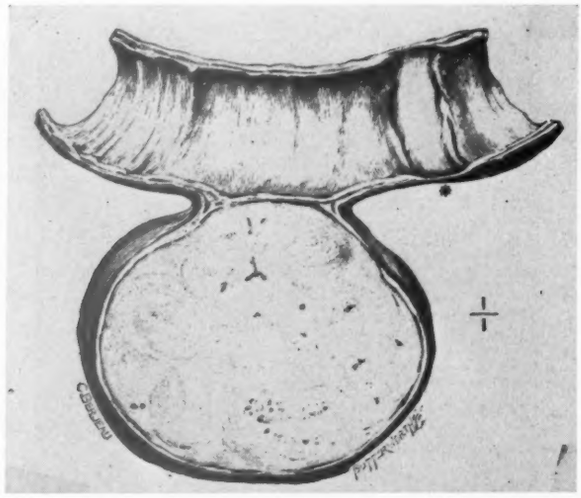

FIG. 18. Intestinal leiomyo(sarco)mas may cause obstruction by occlusion, as well as by intussusception. There is also a third modality: volvulus. In the "fibroid of the small intestine" pictured (an obvious extraluminal type), at the thinned-out stripe, marked with an asterisk (*), Bland-Sutton remarked that "all the coats of the gut, except the serous, yielded under torsion." This specimen, which came from a man aged forty-eight, is preserved in the museum of the Royal College of Surgeons in London [*27*]. (Reproduced through the courtesy of the John Crerar Library, Chicago.)

ROENTGENOLOGIC FINDINGS

In the 1940's an editorial writer joyously announced the belief that leiomyomas were a tumor with typical roentgenologic appearance [*165*]. This was, however, merely wishful thinking. After specifying the organ, and within the organ the precise location of the tumor, there will be obvious differences in the appearance of the neoplasm, depending on whether it is intraluminal, intraparietal (submucous or subserous) or extraluminal. Indeed, it seems reasonable to describe a "typical" appearance for each and every one of these different types [*62*]. This would explain why the roentgenologic features listed by various authors were applicable mostly (if not only) to the cases under consideration in that particular report. Nevertheless, a few generalizations may be allowed.

"Alimentary" smooth muscle tumors, as seen on roentgenologic examinations, exhibit (1) a *benign* appearance, usually present also in sarcomatous varieties, (2) *calcification*, (3) *ulceration*, and (4) in the absence of massive bleeding or acute ileus, a *discrepancy between the extent of involvement and the relatively innocuous clinical symptomatology*. Two or more of these signs, when found concurrently [*2*], are more suggestive

FIG. 19. A forty-three year old Negro was admitted to Cook County Hospital on June 3, 1960, for chest pain and dizziness (which he had had for several years). A blood count revealed hypochromic, microcytic anemia. During his hospital stay, mild dysphagia developed. Barium swallow yielded this roentgenogram, which is as typical of esophageal leiomyo(sarco)ma as anything ever so labeled. Biopsy (slides examined by Szanto) demonstrated a squamous cell carcinoma. There are no truly characteristic roentgenologic signs. The findings are, at best, suggestive. To this day, a positive diagnosis of tumor can be made only on the basis of histopathologic examination; this is an oft forgotten commonplace. (Reproduced through the courtesy of Dr. Hildegard Schorsch.)

than one. (Fig. 19.) Still, none (or any combination of them) should be regarded as pathognomonic. Other tumors [*222*], including epithelial malignancies [*163*], can simulate any of these appearances.

It may be of interest to note that the calcification in gastric myomas may be picked up on fluoroscopy [*142*], sometimes only after insufflation of air, so as to provide a "negative" background [*130*].

When the tumor is in the gastric fundus, the gas bubble will occasionally outline it on routine upright views of the chest. This can be "accentuated" by ingestion of a carbonated drink [*4*] (e.g., "coca cola" as suggested in Argentina), with or without barium meal.

In 1930, in Australia, an elderly patient had no roentgenologic examination, because she refused treatment [*299*]. Today, the indications for barium study of (any segment of) the gastrointestinal tract are part of the general philosophy of medical diagnosis. The recent radiation scare should not deter one from ordering such an examination, provided it appears clinically indicated.

ENDOSCOPY

Whenever feasible, direct visualization of the tumor (area) is of obvious advantage. For intraluminal types it may also offer a means of biopsy, with the attendant histologic confirmation (or exclusion).

Esophagoscopy, for instance, is of importance not only in the polypoid and/or ulcerated types [*265*], but also in the bulging subserous or submucous tumors [*298*], or simply to rule out other (intrinsic) esophageal lesions [*245*]. The same goes for proctoscopy [*206*] and gastroscopy [*241*].

The first gastroscopic description of leiomyosarcoma [*242*] was offered in 1942 by the Viennese gastroscopist *par excellence* Rudolf Schindler (who, at the time, was in Chicago but is now in Brazil). Very few people know, however, that the first gastroscopic description of leiomyoma was recorded in 1922. It had been performed by the Danish gastroenterologist Carl Urban Maaløe on a fifty-one year old male patient with ulcer on the greater curvature, and was presented in a paper [*252*] by Knud Iver Assens Secher, a sportive cardiologist from Copenhagen.

At one time an odd relationship of cause-effect was assumed to exist between leiomyoma and diverticulum. Older references could be unearthed [*297*], but the first to ideate such a relationship (both in the stomach and in the intestines), in 1922, was Max Puskeppelies [*224*], a pathologist in Berlin. His hypothesis (concurrent embryogenesis of leiomyoma and diverticulum), accepted by Nauck [*200*], and rejected by Cleve [*52*], is seldom recalled, mainly because of few corroborative findings (in the esophagus [*164*], stomach [*111*] or jejunum [*34*]). Simple coincidence is a valid explanation for such concomitance.

There is one report [*273*] of visualization of an exogastric tumor through a peritoneoscope. This type of endoscopy, very adequate during its time of glory (1920–1940), cannot match the advantages of today's fairly safe open laparotomy.

SUMMARY AND CONCLUSIONS

Smooth muscle tumors occur all along the alimentary canal. The order of relative frequency, by organs, is stomach, esophagus, small

intestine (jejunum, duodenum, ileum), colon, rectum, mouth, pharynx. In the past they often went unrecognized, therefore available figures of percentual incidence are of little or no significance.

"Digestive" smooth muscle tumors can be identified in retrospect in some autoptic reports prepared between the Renaissance and Virchow. The first comprehensive review of these tumors was compiled by Virchow in 1863. After Virchow about 2,000 (and perhaps as many as 2,500) esophagogastrointestinal leiomyo-(sarco)mas have been reported in the universal literature.

Palpable, nodular, but asymptomatic smooth muscle tumors occur quite frequently within the walls of the alimentary canal (*interstitial* type). The comparatively few which increase in size (*intramural*, *intraparietal*), grow either toward the outside (*subserous*) or toward the inside (*submucous*). Peristalsis may extrude them (*extraluminal* type) or intrude them (*intraluminal*), whereupon they acquire a polypoid appearance, sessile or pedunculated. These tumors are usually solid (but may be cystic), well demarcated (never encapsulated), occasionally multiple. Often they ulcerate, bleed and/or calcify.

The "benign" form (leiomyoma) is more frequent (in most tabulations by a ratio of 3:1) than the "malignant" form (leiomyosarcoma). Standard criteria (increased cellularity, anaplasia, atypical mitoses) do not suffice to distinguish the two forms. Microscopically, most of these tumors (including some of those which metastasize, and indeed the metastases themselves) are made of well differentiated smooth muscular elements. By contrast, a benign clinical course, without demonstrable metastases, can take place in the presence of histologically "malignant" smooth muscle neoplasm. At times, only long-term observation (i.e., final outcome) will determine the adequate epithet (benign or malignant). This ambivalent potential has been expressed by the parenthetic title leiomyo(sarco)ma.

During the *pathologic* phase in the history of these tumors, esophagogastrointestinal leiomyo-(sarco)mas were seen only by pathologists, except at the two orifices of the digestive tract. The *surgical* phase started around 1890, when these tumors began to be found on the operating table. Since 1920 efforts are being made to bring about their *clinical* phase, i.e., to learn to recognize them before surgery or autopsy. This is all the more important because resection is often curative, even for so-called leiomyosarcomas.

A positive diagnosis of tumor type can be made only through histologic examination. The symptomatology and roentgenologic findings of "digestive" leiomyo(sarco)mas vary with the type, size and location of the tumor, hence no true generalization can be attempted. Eventually, extraluminal types cause *pressure* symptoms, intraluminal *occlude*, a few submucous and subserous *obstruct* (by intususception or volvulus). The most frequent symptom is *bleeding* from the gastrointestinal tract, with ensuing anemia. The most common roentgenologic features are *benign* appearance (even in leiomyosarcomas), *ulceration*, *calcification*, and over-all involvement more *extensive* than clinically expected.

Today it is within the scope of the *internist* to make a *tentative* diagnosis of "digestive" smooth muscle tumor, on the basis of hematemesis and/or melena, with or without suspicious roentgenologic findings, and to decide if and when, for purposes of biopsy, there is indication for endoscopy and/or exploratory surgery.

POSTEA

To find such a tumor, other than by chance, means first of all to think of it. *The sin of omission in diagnosis* (but not in therapy) *is potentially more hazardous than the sin of commission.* Nevertheless, diagnostic aids (card systems, slide rules, electronic computers [*166*]), never will, nor were they intended to, supplant the clinician. When using such an aid, the physician elicits the patient's subjective and objective findings, "feeds" the data into the machine, and receives a more or less complete but indiscriminate listing of diagnostic possibilities: from these he then selects the most likely one.

Logan Clendening (1884–1945), the medical philosopher from Kansas City, once remarked that " . . . the most brilliant diagnosticians . . . are the ones who do remember, and consider the most possibilities!" Some day, computers may do our remembering. When pertinent, esophagogastrointestinal leiomyo(sarco)-mas would then be listed unerringly, but clinicians will always be needed to keep things in proper perspective.

Acknowledgment: The following references include less than one-third of the estimated total of pertinent titles. Their consultation was greatly facilitated by the gracious help received from the

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Clinicopathologic Conference

Clonorchis Sinensis and Intractable Heart Failure

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A WHITE housewife (C. W.), fifty-two years of age, entered the Barnes Hospital for the second time on February 27, 1960, with the complaint of heart trouble, fever and chills; she died on April 6, 1960.

The patient's first admission to Barnes Hospital was from July 14, 1959, to August 23, 1959. The patient had been in good health until March 1959 when dyspnea developed on exertion and orthopnea. Diuretics were administered and she lost 20 pounds in weight. She had been admitted to the Jewish Hospital in April 1959 because of progressive increase in her symptoms. Physical examination at that time revealed rales in the lungs, a loud pulmonic second sound, hepatomegaly and pedal edema. Roentgenographic examination of the chest was described as showing cardiac enlargement and pulmonary congestion. The thymol turbidity was 12 units, cephalin cholesterol flocculation 3 plus, and bromsulphalein retention 7.9 per cent. The patient was discharged from the Jewish Hospital on May 12, 1959, with instructions to take digitalis and chlorothiazide. Following discharge she had progressively increasing dyspnea, orthopnea, anorexia, vomiting and cough productive of blood-streaked sputum. There was no history of fever, night sweats or arthralgia.

On physical examination there was stasis dermatitis of both lower extremities, dullness and rales in the bases of both lungs, cardiac enlargement with a loud pulmonic second sound, a systolic murmur at the apex and along the left sternal border, abdominal distention, hepatomegaly, shifting dullness with a fluid wave in the abdomen, 2-plus pitting edema of both legs, and bilateral clubbing of the fingers.

The laboratory data were as follows: The blood count was normal except for a hemoglobin of 11.4 gm. per 100 cc.; examination of the urine, stool and results of serologic tests for syphilis were negative. Cephalin cholesterol flocculation was 2 plus; thymol turbidity 10.3 units; latex agglutination reactive; antistreptolysin-O titer 400 units; serum bilirubin, protein and alkaline phosphatase were normal. Three lupus erythematosus preparations were negative. Serum electrophoresis was within normal limits. The venous pressure was 223 mm. saline, and the arm-to-tongue circulation time was prolonged to thirty-seven seconds. Sputum smears for acid-fast bacilli and sputum cytology were negative. A cardiac series revealed probable congestive heart failure, minimal bilateral pleural effusions and left ventricular enlargement. Three electrocardiograms were interpreted as showing an abnormal form of ventricular complex compatible with digitalis effect, and a questionable old anteroseptal myocardial infarct. A skin biopsy specimen demonstrated chronic inflammation. A gingival biopsy specimen demonstrated focal chronic inflammation. No amyloid substance was seen.

The patient was treated with digitalis, low salt diet and diuretics; she lost 13 pounds during her hospital stay. During the latter part of her hospitalization, the patient was treated with dicumarol because of the possibility that her cardiac disease might be related to multiple pulmonary emboli.

The patient's second admission to Barnes Hospital was on February 27, 1960. Following previous discharge from the hospital, the patient was treated with digitalis, low salt diet, hydrochlorothiazide, potassium supplements, dicumarol, and limited activity. On this regimen her

cardiac disease was well compensated. Early in February a skin rash developed thought to be due to chlorothiazide. About two and a half weeks prior to admission she had sudden fever, shaking chills and profuse sweating. Her temperature rose to 101° to 102.5°F. nightly and was associated with a purulent and sometimes bloody nasal discharge, sinus tenderness and headache. She was originally treated with salicylates without benefit. Because her symptoms persisted, she was admitted to the hospital. She denied cough, chest pain, back pain, dysuria and hematuria. She was having no dyspnea on exertion, paroxysmal nocturnal dyspnea or edema.

The patient had been hospitalized in 1954 for bilateral saphenous vein stripping; in 1957 for diarrhea (a "complete gastrointestinal work-up" was negative); in 1959 for a leg ulcer. There was a questionable allergy to strawberries. She described a liver infection which developed after eating raw fish when she was living in Shanghai between 1939 and 1946. The patient had had clubbing of her fingers as long as she could remember. Multiple teeth had been extracted about five weeks prior to her first admission to Barnes Hospital. There was a history of intermittent pain and swelling of the proximal interphalangeal joints of her hands for an unknown length of time.

The physical examination at this time revealed a temperature of 37.6°C., pulse of 74 per minute, and a blood pressure of 80/64 mm. Hg. The patient appeared malnourished and chronically ill. The skin was pale and thin. Mild tenderness was present over the maxillary and frontal sinuses. The nasal turbinates were congested bilaterally. Examination of the heart and lungs revealed a few basilar rales, cardiac enlargement and a regular rhythm. The pulmonic second sound was louder than the aortic second sound; the sounds were of good quality and there was a grade 2–3/6 mid-systolic murmur at the apex. No friction rubs were audible. The liver was palpable 3 cm. below the right costal margin, and there was evidence of fluid in the abdomen. Bilateral varicosities were present in the lower extremities with stasis dermatitis. Clubbing of the fingers was present.

The laboratory data were as follows: Blood count on admission showed the hemoglobin to be 9.2 gm. per cent, white blood cell count 4,200 per cu. mm. with a differential of 6 per cent band forms, 62 per cent segmented neutrophils, 29 per cent lymphocytes and 3 per cent monocytes. The hematocrit was 30 per cent; sedimentation rate 32 mm. per hour. The urinalysis showed a specific gravity of 1.010, reaction 7.5, protein 3 plus, sugar negative, 8 to 10 white blood cells per high power field in the centrifuged sediment. Stool guaiac and blood Kahn reactions were negative. The blood count on February 29 was hemoglobin 11 gm. per cent, hematocrit 33 per cent, white blood cell count 4,550 per cu. mm. with a differential of 1 per cent eosinophils, 1 per cent band forms, 40 per cent segmented neutrophils, 52 per cent lymphocytes and 6 per cent monocytes, mean corpuscular volume 93 cu. μ, mean corpuscular hemoglobin 31 $\mu\mu$g., mean corpuscular hemoglobin concentration 33 per cent. The blood count on March 4 was hemoglobin 9.5 gm. per cent, hematocrit 31 per cent, red blood cell count 3,340,000 per cu. mm., white blood cell count 4,850 per cu. mm. with a differential of 1 per cent basophils, 1 per cent metamyelocytes, 3 per cent band forms, 70 per cent segmented neutrophils, 15 per cent lymphocytes and 10 per cent monocytes. The reticulocyte count was 5 per cent, platelet count 250,000. The blood count on April 5 was hemoglobin 11.4 gm. per cent, hematocrit 35 per cent, white blood cell count 13,450 per cu. mm. with a differential of 2 per cent metamyelocytes, 31 per cent band forms, 57 per cent segmented neutrophils, 10 per cent lymphocytes; 4 nucleated red blood cells per 100 white blood cells. There was marked polychromasia and anisocytosis of the red blood cells, and very heavy toxic granulation of all white blood cells.

Blood chemical determinations on February 29 were blood urea nitrogen 29 mg. per cent, fasting blood sugar 106 mg. per cent, calcium 8.7 mg. per cent, phosphorus 3.8 mg. per cent, alkaline phosphatase 6.6 units, cholesterol 171 mg. per cent, amylase 76 units; serum glutamic oxaloacetic transaminase 43 units, serum glutamic pyruvic transaminase 12 units, cephalin cholesterol flocculation 4 plus, thymol turbidity 18.3 units, serum bilirubin 1 mg. per cent with 0.6 mg. per cent indirect and 0.4 mg. per cent direct, uric acid 5.2 mg. per cent, bromsulphalein 10.7 per cent retention after forty-five minutes, urine sodium 4.6 mEq. per L., potassium 22.7 mEq. per L., chloride 1.0 mEq. per L., with a total urine volume of 1,240 cc. Latex agglutination was reactive. The lupus erythematosus preparations were negative. A few results

TABLE 1
LABORATORY DATA

Date	Blood Urea Nitrogen (mg. per cent)	Serum (mEq./L.)				Total Serum (gm. per cent)		
		Sodium	Potassium	Chloride	Carbon Dioxide	Protein	Albumin	Globulin
February 29	29	125	3.2	73	39.0	7.4	3.4	4.0
March 3	...	131	3.6	80	28.0	...	...	...
March 21	22	140	4.6	97	27.3	6.6	3.5	3.1
April 4	...	124	3.4	88	25.9	...	...	...

with serial determinations may be seen in Table 1. Serum electrophoresis performed on March 3 was interpreted as showing normal albumin, normal alpha$_1$ globulin, slightly decreased alpha$_2$ globulin, normal beta globulin, increased gamma globulin. Urinalysis on March 9 showed a specific gravity of 1.009, protein 1 plus and a full field of white blood cells per high power field.

Bacteriologic cultures were reported as follows: nasal, one colony of white staphylococcus; throat, pure growth of alpha hemolytic streptococcus; sputum, heavy growth of candida, not albicans; four blood cultures and one urine culture, no growth. Three sputum smears for acid-fast bacilli were negative. Examination of stools for parasites revealed Clonorchis sinensis ova on two occasions. Brucella, tularense, salmonella typhi O, and groups C and E agglutinins were negative.

On the day of admission the patient's temperature rose to 37.9°C.; cultures of the blood, nose, throat, sputum and urine were obtained. The venous pressure was 140 mm. saline, and the arm-to-tongue circulation time was twenty-four seconds. Administration of digitalis and dicumarol was continued. Roentgenographic examination of the paranasal sinuses was within normal limits. Chest roentgenograms taken on admission were interpreted as revealing a slight increase in the mottled pulmonary infiltration over that which was seen on February 12. The heart was enlarged; pericardial effusion was considered a possible cause of the cardiomegaly. Bilateral minimal pleural effusions and some pulmonary congestion were also described, along with hepatosplenomegaly. Electrocardiographic interpretation was sinus bradycardia, abnormal form of ventricular complex compatible with anterior myocardial ischemia, digitalis effect and a questionable old anteroseptal myocardial infarct. A vectorcardiogram revealed intraventricular conduction delay, anterior myocardial ischemia and digitalis effect. Results of histoplasmin, blastomycin, coccidioidin and intermediate purified protein derivative skin tests were negative.

The patient was given potassium orally intermittently during her hospital course. Bilateral maxillary sinus puncture and irrigation were performed with a clear return. The consulting otolaryngologist thought the patient had a subsiding subacute rhinosinusitis which probably was not the cause of her long fever and generalized symptoms. On March 4 a hemotology consultant examined the patient. Bone marrow removed by aspiration was very cellular with slight increase in lymphocytes and reticulum cells; the myeloid:erythroid ratio was 100:34.5; no diagnosis was made. The hematology consultant believed dicumarol therapy should be discontinued and a liver biopsy should be performed. The possibility of a granulomatous infection or a malignant lymphoma was suggested. On March 12 a needle liver biopsy was performed. No diagnosis could be made. No pericardial fluid was obtained by pericardiocentesis on March 18.

On March 19 chloroquine therapy was begun because C. sinensis ova were found in the stool. Three days later the patient's temperature, which had been elevated since admission, became normal and remained so until three days before her death. On March 23 dicumarol therapy was reinstituted. A repeat chest roentgenographic examination revealed progressive interval clearing of the infiltrates of the lower lobes, without significance change in cardiac size or contour, persistent elevation of the dia-

phragm bilaterally and intrapulmonary nodular mottling. On March 28 the house officer was called to see the patient because of acute dyspnea. Rales at the bases of both lungs and a diastolic gallop rhythm were heard. An electrocardiogram revealed an abnormal form of ventricular complex, compatible with digitalis effect, question of old anteroseptal myocardial infarction and clockwise rotation. Anxiety and dyspnea persisted. On April 1 an electrocardiogram revealed paroxysmal atrial tachycardia with 2:1 atrioventricular block, multifocal ventricular premature contractions, question of old anteroseptal myocardial infarction, digitalis effect and suggestion of digitalis excess. The serum potassium value at this time was 2 mEq. per L. Potassium chloride was given intravenously and the cardiac rhythm reverted to normal sinus rhythm. The patient's condition began to deteriorate, however. Cyanosis, tachypnea, weakness and tachycardia were prominent.

On April 3 the patient passed a bloody stool, was nauseated, vomited and had vague lower abdominal tenderness. The hematocrit was 32 per cent. Adrenal cortical steroids were added to the therapeutic regimen and vitamin K was given intravenously. During the next few hours the lower abdominal pain became steady, increasingly more severe, and was associated with tenderness in the right and left lower quadrant. A roentgenographic examination of the abdomen was interpreted as showing air in the biliary tree and an adynamic ileus, thought to be secondary to superior mesenteric thrombosis. The following day the administration of adrenal cortical steroids was discontinued and tetracycline therapy was started. A surgical consultant was asked to see the patient. A small amount of straw-colored fluid was obtained by paracentesis; culture of the peritoneal fluid was sterile.

On the morning of April 5 the patient passed another large bloody stool. The blood pressure dropped to hypotensive levels and the pulse became rapid and weak. The patient's abdomen became distended and taut. The temperature rose to 38.9°C. An electrocardiogram revealed sinus tachycardia with a rate of 150, abnormal form of ventricular complex compatible with the changes associated with sinus tachycardia and/or digitalis effect, and question of old anteroseptal myocardial infarction. A few hours later an exploratory laparotomy was performed. Infarction of the ileum and jejunum, presumably secondary to mesenteric artery occlusion, was found. A small bowel resection was carried out. Culture of the peritoneal fluid resulted in no growth on blood agar or McConkey plates, but an unidentified gram-positive rod grew anaerobically from thioglycolate broth. Postoperatively, epidural anesthesia was maintained. The patient's blood pressure remained low, in spite of adrenal cortical steroid therapy, and on the morning of April 6, 1960, she died.

CLINICAL DISCUSSION

DR. CARL V. MOORE: This woman was fifty-two years of age at the time of her death. In 1939 she fled from Nazi Germany to Shanghai, where she lived until 1946. While in Shanghai she became infected with C. sinensis from eating raw fish. In 1946 she moved to Montevideo for a few years before coming to the United States. Except for episodes of diarrhea and trouble from varicosities in her legs, she remained well until about March 1959. Clubbing of her fingers had been present for as long as she could remember. Her first symptoms were those of cardiac failure associated with pulmonary congestion. During her admission to the Jewish Hospital in April and May of 1959, cardiomegaly and a loud pulmonic second sound were detected; results of hepatic function tests were abnormal. Despite therapy for cardiac failure, she did poorly, having blood-streaked sputum on several occasions. In June, five teeth were extracted. Here, in July and August, she was found again to be in failure, had hepatosplenomegaly and ascites, which gradually responded to therapy. For five or six months she did reasonably well, but early in February 1960, she had fever, chills, profuse sweating and clinical evidence of sinusitis. Again the heart was enlarged with an accentuated pulmonic second sound, the liver was palpated 3 cm. below the costal margin and ascites was detected. A moderate normocytic anemia, abnormal reaction to hepatic function tests, and the electrolyte changes of hypochloremic alkalosis were found. C. sinensis ova were identified in her stool by Dr. Tsuchiya. Dicumarol therapy was interrupted for an unsuccessful liver biopsy. Nucleated red cells were found in the peripheral blood. Results of bacteriologic studies were largely negative. Chloroquine therapy was given, and the patient seemed to improve. However,

she was found at various times to have a gallop rhythm, sinus tachycardia, paroxysmal atrial tachycardia and 2:1 atrial ventricular block. The serum potassium was low, and normal rhythm was restored after the intravenous administration of potassium chloride. About three weeks after the attempted liver biopsy, the patient passed bloody stools, was nauseated, vomited, had lower abdominal tenderness and changes of adynamic ileus. Two days later she passed another bloody stool, became hypotensive, and underwent laparotomy. A large part of the small bowel was thought to be infarcted and was removed. Surgical biopsy specimens were consistent with the diagnosis of infarction. The ascitic fluid was foul; an unidentified gram-positive rod grew anaerobically from thioglycolate broth, but from no other culture medium. Her temperature continued to rise despite supportive therapy, and the patient died the morning after her operation.

Dr. McAlister, will you discuss the roentgenograms?

Dr. William H. McAlister: The initial chest roentgenogram taken on July 15, 1959, demonstrated an intact bony thorax; the heart exhibited generalized enlargement without detectable intracardiac calcification. Minimal calcification was present in the aorta and some small right hilar lymph nodes were seen. Pulmonary congestion, evidence of pulmonary edema and blunted costophrenic angles were present. The blunting in part represented old pleural disease. The spleen was enlarged.

A film taken on February 28, 1960, revealed much the same, namely, a generalized type of cardiac enlargement and pulmonary congestion. I think this primarily represented cardiac disease with secondary pulmonary changes; I could not recognize a pulmonary infarct or any thrombosis of major vessels. In differentiating between some form of myocardiopathy versus fibroelastosis, the former would be favored on the basis of the configuration and lack of left atrial enlargement. This is not a reliable index, however.

An obstruction series dated April 4, 1960, showed dilatation of the small bowel with a little dilation of the right colon. There was separation of gas-filled small bowel loops by edematous walls and peritoneal fluid. These findings in the abdomen are the most common ones seen in mesenteric vascular occlusion. The extremely interesting finding was the gas in the portal vein. (Fig. 1.) There was a fine branching

Fig. 1. Fine branching pattern of gas in portal vein. When air is in the biliary tree, the caudal flow of bile tends to prevent the fine proximal biliary ducts from filling with air; gas in the portal vein tends to be carried to the fine portal channels.

pattern of the gas.* When air is in the biliary tree, the caudal flow of bile tends to prevent the fine proximal biliary ducts from filling with air; whereas gas in the portal vein tends to be carried to the fine portal channels. The etiology has not been established, but evidence indicates that septicemia caused by gas-forming enteric organisms accounts for at least some cases. The frequency of congestion, distention and necrosis of the intestine accompanying this condition may help support this theory. Other observers believe that breakdown of the bowel wall, as in mesenteric infarction, disrupts the integrity of the endothelium and gas is carried from the bowel to the portal vein. All patients described have died shortly after recognition of the intravascular gas.

Dr. Moore: Since we rarely have a case to present at one of these conferences in which the patient has a liver fluke, I have asked Dr. Garfinkel to review C. sinensis infections briefly for us. Dr. Garfinkel had considerable experience with this problem while he was serving in Korea as a member of the Joint Dysentery Unit of the Commission on Enteric Disease.

Dr. Bernard Garfinkel: C. sinensis, or the Chinese liver fluke, is a member of the trematode

* Wiot, J. F. and Felson, B. Gas in the portal venous system. *Radiology*, in press.

family of flat worms. The organism is found in the Far East; it is endemic in many areas there: China, Korea, Indo-China and Malaya. The adult worm is 10 to 25 mm. in length and 3 to 5 mm. in width. The worm is a true hermaphrodite, having both an ovary and testis. It gets its name, actually, from the very characteristic branched testis. The name C. sinensis means branched testis. The organism goes through many stages and has a very interesting life cycle. The adult worm is found only in the definitive host, which is usually man but may also be the dog.

The mature worm lies in the small bile radicles of the liver in man or in the dog. The eggs are excreted in the bile and then passed on to feces and into the water of various streams. The egg is embryonated at the time it is deposited into the water. In some of the flukes, the embryo escapes and becomes a cilliated, free-swimming myricidium. This organism does not hatch in the water, but the entire egg is then ingested by the snail which is necessary for its next stage of development. The development of the organism then takes place in the snail, where it goes through two generations. The first generation is the sporocyst; the second generation is known as the redia, which then forms the tailed cercaria. The cercaria is discharged from the snail into the water. This is a free-swimming form; and the organism finds its intermediate host, a fresh water fish, and is deposited beneath the scales of the fish; the tail drops off, and the cercaria then burrows into the tissue of the fish where it becomes enycsted in the flesh and is then eaten by man or dog, the definitive host. The cycle then begins over again.

The organism escapes from its encysted form in the stomach; it invades the tissue of the duodenum, finds its way into the biliary system and thence into the small bile radicles. In the small bile radicles it produces an intense inflammatory and proliferative change. There is an intense proliferation of the epithelial lining, with polymorphonuclear and eosinophilic infiltrate; another characteristic is the fibrous capsule which forms to encompass the worm and the epithelium of the biliary radicle. The worm, as it lies in the biliary tree, will deposit eggs which are sent into the bile and thence into feces. The egg is light tan with a fairly thick shell; it has a definite operculum at the top, and at the other end there is usually a small spine.

The infection is acquired by eating poorly cooked or uncooked fish. One of the best known epidemics was that which occurred in Shanghai, and apparently this is where this patient was infected. There were apparently some 20,000 Jewish refugees from Nazi Germany in Shanghai, and in March 1946 an epidemic occurred in which it is estimated 20 to 30 per cent of these people were infected by clonorchis from eating pickled fish. The infection itself is usually mild, if there is only one exposure. The usual number of worms found in the liver varies from 20 to 200, but cases have been found in which up to 20,000 worms have been discovered in a single liver. The disease may be so mild that there are no symptoms; or it can progress to intense fibrosis, scarring of the liver, and a picture of severe portal cirrhosis results.

DR. MOORE: An interesting sidelight on that Shanghai epidemic was that fresh-water fish were pickled and sold to the Jewish refugees as pickled herring.

Dr. Shank, can we make a diagnosis of cirrhosis of the liver? It should be emphasized that results of hepatic function tests were abnormal within a month after the signs of heart failure began; that makes it difficult to attribute the hepatic disease to chronic congestion.

DR. ROBERT E. SHANK: From the history as recorded, I would have to assume that this woman did have pre-existing liver disease. This, coupled with the fact that ova were found in the stool on admission, would arouse my suspicion that liver damage was on the basis of the liver fluke. The hepatomegaly was not of great degree. If hepatic involvement was solely on the basis of cardiac decompensation, I would expect that the liver would have been somewhat larger than was observed. In addition, the patient apparently had splenomegaly, at least on one examination. I do not think this was recorded in the protocol. Is that not correct?

DR. MOORE: That is correct; the spleen also appeared enlarged on the abdominal roentgenograms.

DR. SHANK: There was no description either of venous anastomotic channels in the abdominal wall, which would afford other evidence of portal hypertension and hepatic fibrosis. The laboratory evidence of hepatic parenchymal dysfunction was not that indicating an active process. For instance, the transaminase values were not increased and serum albumin was described as being normal. On the other hand, her cephalin cholesterol flocculation reaction was 4 plus, and

the thymol turbidity was elevated in major degree. In addition, there was increase in gamma globulin and bromsulphalein retention. With these observations, I would deduce that the patient did have chronic hepatic damage, influenced unfavorably by the occurrence of cardiac decompensation. With the finding of ova of the liver fluke, I believe that we must suspect that the primary hepatic disease was on this basis. Corroborating this opinion is the description in the literature of the existence of ova for periods as long as twenty to twenty-five years after acute infection, with hepatic disease discovered either very late in its course or at autopsy.

DR. MOORE: Dr. Massie, one of the diagnostic problems, and the chief problem so far as this patient was concerned, was her heart failure which appeared rather suddenly without any obvious cause. There was no clinical evidence of pericardial involvement. We are faced with the old task of trying to differentiate coronary artery disease from idiopathic cardiac hypertrophy and all the related syndromes. Will you review and interpret the electrocardiographic abnormalities?

DR. EDWARD MASSIE: The two types of cardiac disease we must consider in view of the murmurs and an abnormal electrocardiogram are valvular involvement and coronary disease; yet I am fairly sure in my own mind that she had neither significant coronary disease nor a valvular lesion. All the electrocardiograms were very similar. They showed Q waves in leads V_1 and V_2 and a small R wave in lead V_3. It is not an easy problem to decide whether the Q and small R waves in these leads were due to an old anteroseptal infarction, to emphysema or to physiologic or positional factors. First of all, it is not positional because we have a number of electrocardiograms with the same findings, so we know the technicians took the record with the proper chest positions. I could not rule out an anteroseptal infarction, but it is always hazardous to assume that these Q or small R waves would have this significance without a positive history. Marked emphysema could have been the cause, but does not seem to be present here. If we had noted electrocardiographic changes over the course of the year or more during which the patient was followed, we could suspect coronary artery disease; but we saw no such evidence. As the patient's condition became worse, we had an episode suggesting that she had pulmonary emboli. Some clockwise rotation appeared in the electrocardiogram. This finding, although only mildly suggested in the record, could be in keeping with acute cor pulmonale. However, we have nothing else to substantiate that diagnosis, such as right axis deviation or P pulmonale. Toward the end of the patient's life, paroxysmal auricular tachycardia with block appeared. The clinicians rightly decided that the patient had had too much digitalis, determined the serum potassium level and found it low. They gave the patient potassium and in the next record sinus rhythm was re-established.

To summarize, it does not appear that this patient had valvular disease, coronary involvement or a large number of pulmonary emboli.

DR. MOORE: Dr. Owen, will you continue the discussion of the differential diagnosis of the cardiac lesion?

DR. JAMES W. OWEN: I could find no completely satisfactory diagnosis for this woman. I think I would agree with Dr. Massie that simple arteriosclerotic heart disease is unlikely. Subendocardial fibrosis or fibroelastosis should be given serious consideration as should idiopathic myocarditis, both of which could account for many of the features that this woman presented. A less common possibility is that of beriberi heart disease, which in its chronic form can produce a very peculiar clinical picture. One other intriguing possibility, with the pulmonary infiltration and the liver findings, is the question of Boeck's sarcoid with involvement of the heart. I think there are objections to all of these diagnoses, but these are conditions that I think should be seriously considered.

DR. MOORE: Dr. Parker, is it conceivable to you that this patient had a form of congenital heart disease? She said that her fingers were clubbed for as long as she could remember. Does subacute endocarditis seem likely?

DR. BRENT M. PARKER: It is certainly conceivable that she did have congenital heart disease at this age; a number of patients have been discovered to have such disease in their fifties and sixties, and some have actually had corrective surgery.

DR. MOORE: When clubbing occurs on the basis of congenital heart disease, is not the patient usually cyanotic?

DR. PARKER: I would think that she would have had cyanosis if she had clubbing due to congenital heart disease. I would also think that someone would have heard a murmur and suspected heart disease many years before.

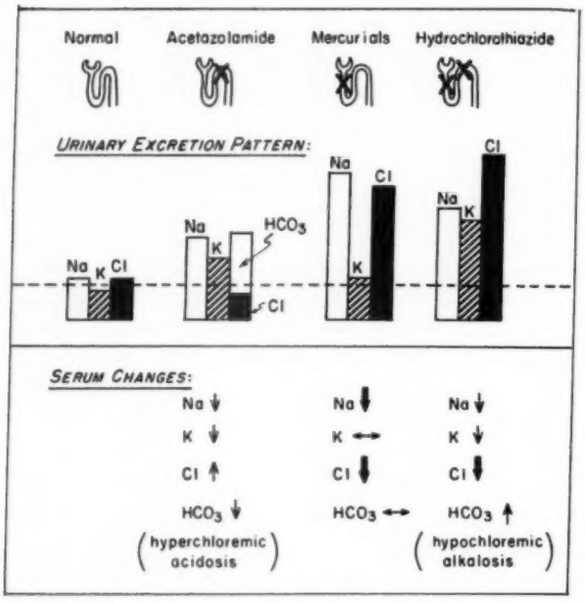

FIG. 2. Schematic pattern of urinary and serum electrolytes following various diuretic agents.

Therefore, congenital heart disease seems extremely unlikely. Endocarditis cannot be entirely excluded. On the other hand, we have a number of negative blood cultures, and peripheral embolic phenomena and changing heart murmurs were not described. My diagnosis would also be one of the diseases in the myocarditis group. I do not see how one can separate the various types of myocardiopathy.

DR. MOORE: Dr. Nelson, the physicians who cared for this patient suggested that her heart disease and pulmonary hypertension might be secondary to multiple pulmonary emboli. She certainly did have hemoptysis on at least one or two occasions.

DR. J. ROGER NELSON: I believe this is a possibility; she may indeed have had multiple pulmonary emboli. However, because of the left ventricular enlargement and signs of left-sided failure, I do not think that this was the primary cause of her difficulty. It must have been only a secondary and complicating phenomenon.

DR. MOORE: It still is worth emphasizing, perhaps, that on a good medical service probably the most commonly missed diagnosis is that of single or multiple pulmonary infarcts.

DR. NELSON: There is no question about the frequency with which this diagnosis is overlooked. May I make one comment about subacute bacterial endocarditis? I believe a little more strongly that it is difficult to exclude that diagnosis. She had four negative blood cultures, but 10 to 15 per cent of patients who have subacute bacterial endocarditis will have persistently negative blood cultures. The presence of a negative blood culture may be a bad prognostic sign. Certainly there was anemia, murmur, clubbing, fever, the spleen became palpable and embolic phenomenon occurred terminally.

DR. MOORE: I do not see how the diagnosis could be ruled out. Dr. Sherry, one of the problems which plagued the house officers was the recurrent hypochloremic alkalosis.

DR. SOL SHERRY: There are two points to be made before discussing the electrolyte abnormalities in this patient. First, hyponatremia and hypochloremia may be associated with any chronic edematous state, particularly when the patient has been maintained on a low salt diet and given fluids *ad libitum*. Second, in those patients who also are given diuretics at frequent intervals and for long periods of time, acid base imbalances as well as severe electrolyte disturbances may be produced; these disturbances usually vary with the type of diuretic used.

In Figure 2 is schematically shown the three kinds of alterations we ordinarily encounter in clinical situations in which frequent and prolonged diuretic therapy is maintained. At the top is shown the pattern of the urinary excretion of sodium, potassium and chloride (the dotted line which extends across the figure is representative of the normal level); on the bottom the associated serum changes. With acetazolamide, when the major action is in the distal tubule blocking or at least impairing hydrogen ion production, the urine contains somewhat increased amounts of sodium and potassium, but usually reduced amounts of chloride. The extra amount of anion, to compensate for the increased excretion of sodium and potassium, is made up by bicarbonate; the urine, of course, tends to be alkaline. With this type of electrolyte loss, a moderate reduction in serum sodium, potassium and bicarbonate ensues while the chloride level is raised; the result is a hyperchloremic acidosis.

Mercurials primarily block the proximal tubular reabsorption of electrolyte; here we observe that the urine contains larger amounts of sodium and chloride, but there is relatively little change in potassium excretion. As a result, severe hyponatremia and hypochloremia may be induced, but without much change in potassium. With the somewhat equal reduction of sodium

and chloride, the bicarbonate is relatively unaffected.

Hydrochlorothiazide, which this patient received, produces a block at the proximal tubular level and has an effect on the distal tubule as well. The urinary pattern as shown is of a moderately brisk natruresis and kaluresis, and a rather striking chloruresis. As a result, a significant reduction in serum sodium and potassium occurs along with a striking reduction in chloride; an alkalosis of moderate to severe degree may be anticipated as a result of the severe chloride loss. Potassium depletion also contributes to the alkalosis since extracellular hydrogen ions move into potassium-depleted cells, leaving an excess of bicarbonate in the extracellular fluid. The entire effect is to produce the pattern of hypochloremic alkalosis.

Our patient's electrolyte findings are fairly typical of a hypochloremic alkalosis with an associated potassium deficiency; it seems most reasonable to attribute these changes to the prolonged hydrochlorothiazide therapy.

DR. MOORE: Dr. Morrin, do you have any additional comments to make?

DR. PETER A. F. MORRIN: No, except to mention the blood urea nitrogen, which was slightly elevated and is consistent with congestive failure without implying intrinsic renal disease.

DR. MOORE: Now for the terminal episode. Two and a half weeks before this patient came into the hospital, chills, fever and diffuse perspiration developed rather suddenly. All attempts to explain that fever were, I think, moderately unsuccessful, although it was suggested that maybe she had a sinusitis. She was prepared for a liver biopsy; dicumarol therapy was discontinued. Following the liver biopsy, she had the trouble which has been reviewed before, and then what presumably was a mesenteric artery thrombosis developed.

Dr. Owen, are you willing to accept the diagnosis of mesenteric artery thrombosis or embolism?

DR. OWEN: With the other evidence of embolic phenomena that were present in this woman, I think we are on safe ground in assuming that this was also embolic in origin.

DR. MOORE: Dr. Saltzstein, will you make a brief comment about the surgical specimen?

DR. SIDNEY L. SALTZSTEIN: The various specimens we received have been adequately described in the protocol. We received most of the patient's small intestine, which was necrotic. Histologically, the necrosis was of the type we would see with some sort of vascular lesion. We did not receive any actual occluded artery or vein.

DR. MOORE: Dr. McAlister presented a discussion of why he thought this patient had air in the portal vein, and why the air could be explained entirely on the basis of mesenteric artery thrombosis. On the other hand, a gram-positive rod, possibly a clostridium, was found in the ascitic fluid. Dr. Harford, could this woman have had a Welch-bacillus infection?

DR. CARL G. HARFORD: The circumstances of the case are the best evidence we have, since the bacteriologic data are quite inconclusive. Aerobic cultures were negative, and the findings in the thioglycolate broth were confusing. I suppose that the presence of necrotic bowel might suggest that clostridia were concerned, but this is scanty evidence.

DR. MOORE: Dr. Riddick, when the abdominal catastrophe occurred, the house officers wondered whether or not the discontinuation of dicumarol therapy in preparation for the hepatic biopsy had been responsible for a prothrombin rebound or for predisposing this patient to the development of thrombosis.

DR. FRANK A. RIDDICK: This patient was off dicumarol therapy for two and a half weeks so that she had only been back on therapy for three or four days at the time the abdominal crisis occurred.

Physicians dealing with long-term anticoagulant treatment have long suspected that withdrawal of this treatment was attended by a somewhat increased tendency to thromboembolism. The possibility has been given some statistical backing by the studies of Wright's group* who, in a large series, found that the recurrence rate of thromboembolism was highest immediately after an untreated thromboembolic episode, and that the rate of recurrence decreased over the weeks following. When anticoagulant therapy was given, recurrence rates were considerably lower, although the risk of another thrombosis or embolism was still greatest in the week following the initial episode. However, they discovered that in the group treated with anticoagulants, withdrawal of

* CARTER, S. A., MCDEVITT, E., GATJO, B. W. and WRIGHT, I. S. Analysis of factors affecting the recurrence of thromboembolism off and on anticoagulant. *Am. J. Med.*, 35: 43, 1958.

therapy gave an immediate recurrence rate of thromboembolism almost as high as that seen immediately after an untreated thromboembolic episode, and that recurrences in the second to fourth weeks following the withdrawal of therapy were somewhat more frequent than at a comparable time after an untreated thrombosis or embolus.

Our own experience has corroborated this. Of 125 patients receiving long-term anticoagulant therapy in the outpatient department, there were thirteen thrombotic or embolic episodes. Six of the thirteen occurred within two weeks after treatment was stopped either by withdrawing the drug abruptly or by administering large doses of vitamin K. The suggestion has been made that withdrawal of dicumarol produces a rebound hypercoagulable state, but the evidence is not great. There is one study* in which single large doses of dicumarol were given; following the initial depression, the prothrombin level, as measured by the two-stage technic, rose to some 20 per cent greater than before treatment. There is no other convincing evidence. Wright has made the suggestion that the reason an increased incidence of thromboembolism is seen following withdrawal of long-term therapy is due to the fact that there are two independent processes going on contributing to vascular occlusion. One is atherosclerosis; the other, thrombosis. He believes that atherosclerosis might progress unimpeded during the period that thrombosis is being inhibited, so that the vessel gets narrower and narrower. When the drug is withdrawn and return to normal coagulation mechanism occurs, the narrowed vessels are much more likely to be occluded at this time.

Dr. Moore: Are there other comments anyone would like to make? Dr. Chaplin?

Dr. Hugh Chaplin, Jr.: May I ask whether amyloid deposits have ever been described in chronic, long-standing involvement with C. sinensis?

Dr. Moore: Not that Dr. Garfinkel or I have been able to find; neither are there destructive pulmonary or cardiac lesions.

It seems to me that the only cardiac diagnosis we can make is idiopathic cardiac hypertrophy. The patient's failure was sudden in its onset; it was protracted. One could easily imagine that she threw emboli from both sides of her heart, which were responsible for the episodes of pulmonary infarction and, at least for the terminal episode, of possible mesenteric infarction. I think she had chronic liver disease and periportal cirrhosis, and hope the pathologist will be able to show us the C. sinensis worms. The terminal episode was probably mesenteric artery embolus rather than thrombosis. It seems impossible definitely to rule out subacute bacterial endocarditis, sarcoidosis and possibly a number of the other rarer lesions such as fibroelastosis.

* Miller, K. D. and Bayer, W. L. Prothrombin rebound—a response to dicoumarol. Abstract of paper presented before the American Society of Hematologists, Montreal, Canada, November 28–30, 1960.

PATHOLOGIC DISCUSSION

Dr. William S. Medart: This poorly-nourished white woman had a 17 cm. healing mid-line surgical incision. The pleural cavities were obliterated by thin fibrous adhesions. There was atelectasis of both lower lobes and accumulations of mucoid secretion in the bronchi. The tracheobronchial nodes were enlarged. There were some fibrous pericardial adhesions. The heart weighed only 320 gm., but both ventricles were markedly dilated. The myocardium was slightly pale, soft and flabby, with "tigering" of the papillary muscles. Arteriosclerosis of the coronary arteries was only slight, but was moderate in the aorta.

About 500 cc. of serosanguinous fluid was present in the peritoneal cavity and the abdominal viscera were coated with fibrous exudate. There was 50 cm. each of ileum and duodenum that remained of the small intestine, and their walls were edematous and purplish red. The mucosa was covered by exudate. No emboli or thrombi were found in what remained of the mesenteric vessels, which were only slightly arteriosclerotic. The kidneys were slightly reduced in size but otherwise not grossly abnormal. The colon was also edematous and its lumen contained fresh blood clots. In the gastric mucosa were four small acute ulcers. The larger biliary passages were infested with black flukes up to 2 cm. in length. It is estimated that over 100 flukes were present. The only parenchymal change noted was marked chronic passive congestion. The remainder of the organs showed no pertinent gross lesions.

Dr. Robert M. O'Neal: This heart which was described as dilated, but not appreciably hypertrophied, was really quite interesting. Diffuse interstitial fibrosis was widespread. (Fig. 3.) A great deal of fibrous tissue was present

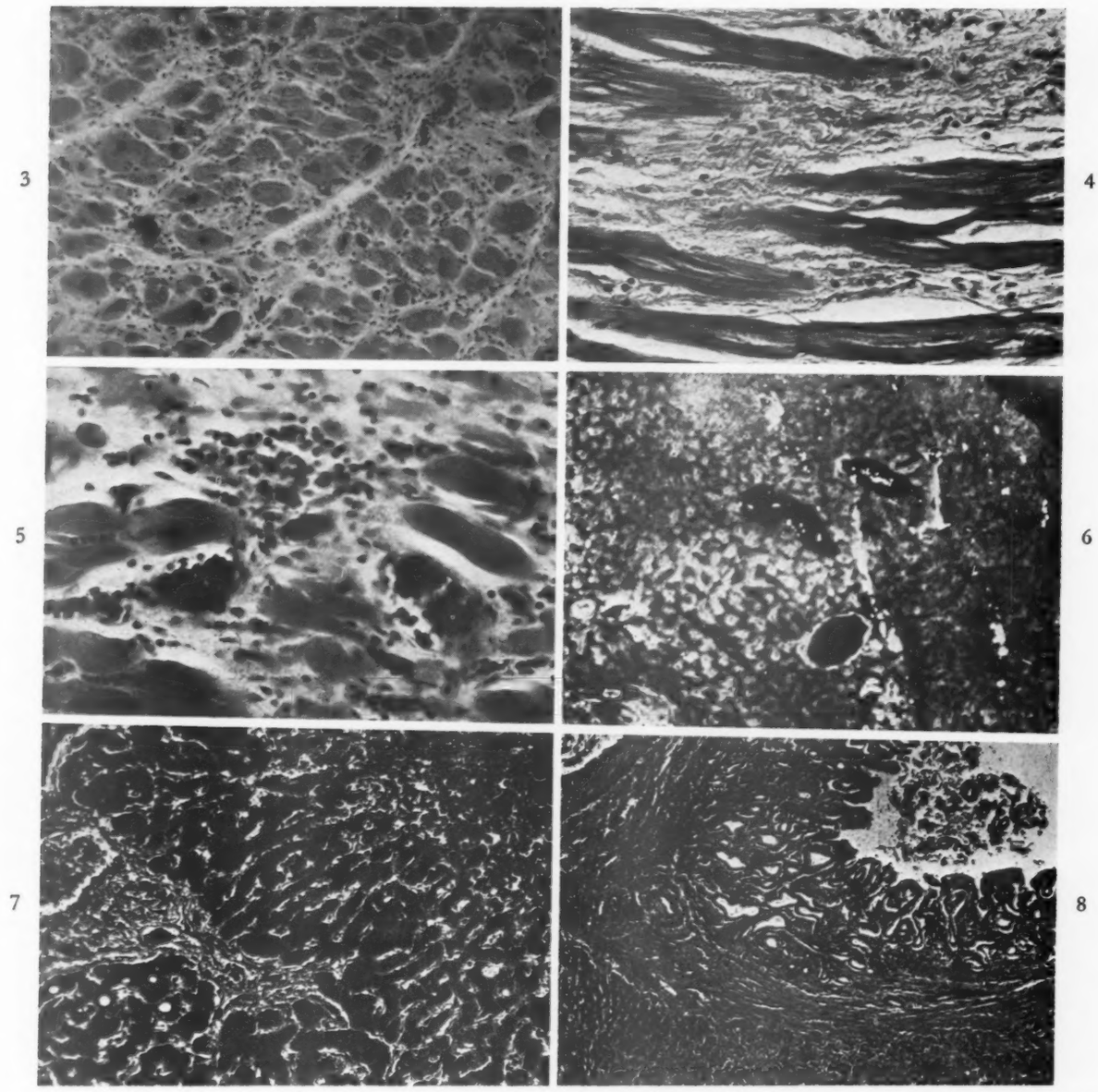

FIG. 3. Myocardium, with separation of muscle fibers by a diffuse, fine fibrosis. Hematoxylin and eosin stain, original magnification × 120.

FIG. 4. Higher magnification to show the collagenous nature of the material between muscle fibers. Phosphotungtic acid-hematoxylin stain, original magnification × 250.

FIG. 5. Another area of the heart to demonstrate the mononuclear cell infiltrate accompanying the fibrosis. Hematoxylin and eosin stain, original magnification × 300.

FIG. 6. Gross photograph of cut surface of liver (magnified) with two flukes (black) emerging from bile ducts.

FIG. 7. Central necrosis of the liver (upper right) and slight periportal fibrosis (left) which was widespread throughout the liver. Hematoxylin and eosin stain, original magnification × 100.

FIG. 8. Marked hyperplasia of the epithelium of a large bile duct, with surrounding fibrosis. Flukes were seen in some of these ducts. Hematoxylin and eosin stain, original magnification × 42.

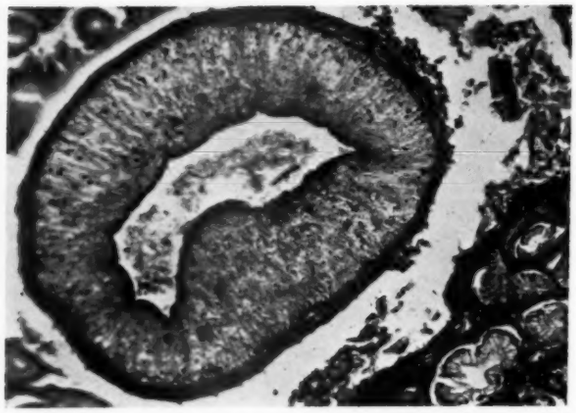

FIG. 9. A portion of a fluke practically filling the lumen of a bile duct. Van Gieson stain, original magnification × 100.

around the muscle fibers and many individual fibers appeared to have been lost. (Fig. 4.) The moderate cellular infiltrate accompanying the fibrosis consisted of mononuclear cells, mostly lymphocytes. (Fig. 5.) The endocardium was slightly thickened in a few areas, but for the most part appeared normal. The pericardium was also focally thickened by fibrous tissue. Very few areas of focal scarring, such as one usually sees with coronary arterial disease, were found. Therefore, all our gross and microscopic evidence indicates that the patient did not have any appreciable coronary artery disease. Such myocardial fibrosis is usually assumed to be the result of a myocarditis, and is designated "isolated myocarditis" without hope of clarifying the etiology. However, in this instance it appears to me that the pathologic findings correspond well with those described late in the course of the disease called "chronic myocarditis of Venezuela," which is thought by most investigators to be a result of Chagas' disease (infection with Trypanosoma cruzi).* Although we have no direct evidence to substantiate this diagnosis, the fact that this woman did spend several years in Latin America prior to the onset of symptoms, makes one strongly suspect that the myocarditis associated with Chagas' disease was the reason for her myocardial fibrosis.

DR. MOORE: Dr. Shank has a comment to make.

DR. SHANK: The area of the world in which Chagas' disease has the highest incidence is in Southwestern Brazil, where the chief cause of death is myocardial disease of this kind. Now, Uruguay is not very far away and I would be very surprised if there was not some of this disease there.

DR. O'NEAL: Apparently it does extend over a fairly wide geographic area. It has also been described throughout Central America.

DR. W. STANLEY HARTROFT. When I was in Montevideo, it had only recently been discovered there.

DR. O'NEAL: The lungs were relatively normal and there was practically no evidence of chronic passive congestion, which indicates that left-sided heart failure was never the dominant feature of her myocardial disease. There were only a few small recent pulmonary thromboemboli and no large ones.

The liver did not suggest even an early cirrhosis. According to Dr. Hou,* who reported 500 cases of C. sinensis infestation from Hong Kong, cirrhosis is not a common result of clonorchiasis but the complication to be feared is the development of cancer of the liver. Parenchymal changes in the liver were limited to marked central congestion with early necrosis indicative of severe right-sided heart failure. (Fig. 6 and 7.) Fatty change was seen around the central areas, which is common in chronic congestion.

The epithelium of many of the bile ducts were markedly hyperplastic, with several "tiers" of glands where we normally expect a simple flat mucosa. (Fig. 8.) Fibrous tissue about these portal spaces was increased moderately in amount and contained a considerable number of lymphocytes. Flukes were occasionally seen in the microsections. Figure 9 shows a large oral sucker that was cut in cross section and was the point of attachment of the larva to the wall. It is interesting to note that although the flukes in this patient were confined to bile ducts, they are sometimes found in the pancreatic ducts. This is used as evidence that the larvae do not feed on bile. In addition, if the larvae are put into bile *in vitro* they die very quickly whereas in blood serum they survive. Apparently, then, the large ventral sucker enables them to feed on blood from the wall of bile ducts and not on the bile itself.

The kidney was not too contributory. Moderate interstitial fibrosis, occasional hyalinized glomeruli and a mild lymphocytic infiltration were considered to be the result of arteriolar narrowing.

* GOULD, S. E. Geographic pathology: chronic myocarditis in Venezuela. *Am. J. Path.*, 36: 533, 1960.

* HOU, P. C. The pathology of Clonorchia sinensis infestation of the liver. *J. Path. & Bact.*, 70: 53, 1955.

The pancreas demonstrated the changes that we see with chronic passive congestion, a halo of normal acini about the islets and then atrophic acini at the periphery.

The remaining ileum showed definite evidence of a chronic enteritis superceding the recent episode of infarction. The intestinal villi were quite thick and contained a marked lymphocytic infiltration. The submucosa and serosa were also markedly fibrosed, and heavily infiltrated by lymphocytes. The patient apparently had some indolent enteritis of long-standing which was not apparent clinically. One possible explanation for this could be long-term partial obstruction of a mesenteric vessel. Of course, there was also acute peritonitis with fibrin over the surface of the peritoneum at all sites.

We think this patient had two separate chronic diseases: a diffuse chronic myocarditis, that might well be the result of Chagas' disease and which led to heart failure; and C. sinensis infestation, which produced the evidences of liver dysfunction noted clinically.

DR. MOORE: She had no evidence of mural thrombi?

DR. O'NEAL: No, although we still suspect that an embolus causing the mesenteric infarction came from the heart, the entire thrombus may have detached itself from the heart. The mesenteric arteries were only slightly atherosclerotic.

The *final anatomic diagnoses* were: Surgical absence of most of the small bowel (100 cm. remained) (history of resection, one day, for intestinal infarction resulting from occlusion of superior mesenteric artery); serofibrinous peritonitis (500 cc. of fluid); acute ulcers in the stomach and remaining ileum; acute ulcers in the stomach and remaining ileum; diffuse interstitial fibrosis of the myocardium, advanced, with slight endocardial fibrosis and pericardial fibrosis, consistent with "chronic myocarditis of Venezuela"; fatty degeneration of the myocardium, moderate; chronic passive congestion of the liver and pancreas, advanced; clonorchiasis of the liver with adenomatous hyperplasia of biliary epithelium.

DISCUSSION

DR. MOORE: I am sure everybody will agree that this was an exciting case with the pathologic material beautifully presented. Does anyone have anything else he would like to say?

DR. W. STANLEY HARTROFT: The relation of cirrhosis to liver fluke infection is by no means an open and shut business. Consensus has swung from one extreme to another. At one time it was thought that every case of cirrhosis-associated Clonorchis was due to the infection and that every case of infection had cirrhosis if you looked for it. Then the consensus swung completely the other way, that in the parts of the world where this infection is seen, protein deficiency is rampant and cirrhosis was due to the protein deficiency. Now opinion is quite divided. Prates,* who is the most prolific writer on this subject, in East Portugese Africa, believes that all his cases of cirrhosis with this infection are due to the infection, and that it is very carcinogenic and responsible for their high incidence of primary cancer of the liver.

DR. MOORE: The cancers are cholangiomas, are they not?

DR. HARTROFT: Yes.

* PRATES, M. D. The etiology of primary cancer of the liver in natives of Mozambique. *Acta Unio contra cancrum,* 13: 662, 1957.

Case Reports

Cushing's Syndrome Associated with Non-Endocrine Neoplasms*

A Review and a New Case, the First with Carcinoma of the Gallbladder

PHILIP W. BRICKNER, M.D.,† MICHAEL LYONS, M.D.‡ *and* S. JACK LANDAU, M.D.§
New York, New York

THE association between malignancy and hyperadrenocorticism is well known in neoplasm of the adrenal cortex and of the pituitary gland [*1*]. Any causal connection between other malignancies and hyperadrenocortism is less clear-cut and may possibly be considered fortuitous. However, since Brown [*2*] in 1928 published a case report, fully characteristic of Cushing's syndrome, with oat cell carcinoma of the lung proved at autopsy, evidence has accumulated suggesting that this relation is more than coincidental.

From 1928 to the present, twenty-eight cases of non-adrenal, non-pituitary malignancy associated with hyperadrenocorticism have been reported. These include twelve oat cell carcinomas of the lung [*2–12*], seven carcinomas of the thymus [*13–18*], five carcinomas of the pancreas four of which were of the alpha cell type [*14,19–21*] and one of the beta cell type [*22*], and one case each of sympathicoblastoma [*23*], thyroid carcinoma [*24*] and ovarian carcinoma [*25*]. The case of carcinoma of the gallbladder reported here is the first of that organ to be noted in this connection.

The validity of establishing some more than coincidental connection between these malignancies and the hyperadrenocortical state associated with them is made clear as follows:

The syndrome of hyperadrenocorticism is not common; approximately 500 cases have been reported to date [*26*]. Review of death rates from neoplastic disease indicates that the occurrence of twenty-eight non-endocrine neoplasms among 500 cases of Cushing's disease would not occur with any likelihood if taken at random. The death rate from neoplastic disease at age forty is fifty per 100,000 of population and rises at age sixty to 500 per 100,000 [*27,28*]. An average death rate of 149 per 100,000 is commonly recognized [*29*].

Further, the types of neoplasm herein discussed are uniquely grouped [*27–29*]. Of the twenty-eight cases, twelve are bronchogenic carcinomas (43 per cent), seven are thymic malignancies (25 per cent) and five are pancreatic carcinomas (18 per cent). In the general population with neoplastic diseases those of the lung make up 11.1 per cent in males and 3.2 per cent in females; those of the pancreas 4.4 per cent in males and 3.2 per cent in females. The incidence of thymic carcinoma is low (less than 0.05 per cent) but is probably higher than that of Cushing's syndrome. As noted by Thorne [*4*] in Great Britain, from 1945 to 1949 there were fifty-three deaths ascribed to thymic tumor, thirty-three to Cushing's syndrome. The percentage differences in neoplasm type among the general population compared to the group discussed here are conclusive, regardless of the definite increasing relative and absolute incidence of lung carcinoma and of statements questioning the rareness of thymic neoplasm [*34*].

Since only five cases of pancreatic carcinoma

* From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the First (Columbia) Medical Division, and the Department of Pathology, Bellevue Hospital, New York, New York. Manuscript received July 5, 1960.

† The work described in this paper was carried out during the tenure of a traineeship of the New York Heart Association. Present address: First Medical Division, Bellevue Hospital, New York, New York.

‡ Present address: Department of Pathology, Bellevue Hospital, New York, New York.

§ Present address: West Haven, Connecticut.

are included in the present group, generalization is prevented but the fact that all were in females and that their average age was thirty-seven years is unusual. Carcinoma of the pancreas is largely a disease of elderly men [*30*]. The twelve lung cases are all histologically characterized as anaplastic and/or oat cell or small cell carcinoma in type, but the expected incidence of these types in bronchogenic neoplasm is 30 to 40 per cent or less [*31,32*].

CASE REPORT

A sixty-two year old Russian-born white woman who spoke no English was admitted to the First Medical Division of Bellevue Hospital on July 21, 1959, with a chief complaint of chest pain of twenty-four hours' duration. There was a questionable past history of hypertension. Three months prior to admission the patient had noted onset of precordial squeezing, non-radiating pain associated with dyspnea on exertion, orthopnea and edema of the ankles. She was treated by a private physician with digitalis and diuretics. The pain continued intermittently until the day prior to admission, when it became unusually severe and unrelenting.

Review of systems revealed a recent loss of visual acuity, and pain in the back and legs associated with weakness. She denied any recent change in her appearance.

On physical examination the patient was an obese, dark skinned, hirsute woman in mild respiratory distress when supine. The suggestion of a "buffalo hump" was present. Temperature was 99°F. per rectum; respirations were 30 per minute and regular; blood pressure was 110 mm. Hg systolic, 70 mm. Hg diastolic; pulse rate was 90 per minute and regular. A grade 2 systolic murmur was audible along the left sternal border. Inspiratory crackling rales were heard at the base of both lungs. The liver was enlarged, the edge felt 4 fingerbreadths below the right costal margin. A well demarcated, slightly tender mass was felt in the region of the gallbladder. Slight pitting edema of the ankles was noted.

The initial white blood cell count was 12,000 per cu. mm., with 86 per cent polymorphonuclear leukocytes, 12 per cent lymphocytes and 2 per cent monocytes. The erythrocyte sedimentation rate was 35 mm. in one hour and the hematocrit was 50 per cent. Urinalysis revealed a specific gravity of 1.020; albumin and sugar were absent; the urinary sediment contained 3 to 5 white blood cells per high power field. Electrocardiogram demonstrated sinus tachycardia, prolonged P-R interval, non-specific S-T and T wave changes, and complete right bundle branch block pattern. A chest roentgenogram showed the heart to be moderately enlarged and a small amount of pleural fluid at the base of the left lung.

Blood urea nitrogen was 40 mg. per 100 ml.; total protein was 6.9 gm. per 100 ml. with albumin of 4.2. Alkaline phosphatase was 3.8 Bodansky units. The reaction to the cephalin cholesterol flocculation test was negative. Serum cholesterol was 480 mg. per 100 ml., with esters of 340 mg. Fasting blood sugar was 125 mg. per 100 ml. Serum sodium was 145, potassium 3.7, chloride 94 and carbon dioxide 36.8 mEq. per L.

The diagnosis of myocardial infarction was made and the patient was treated with bed rest, warfarin (Coumadin®), anticoagulants, diuretics and digoxin 0.5 mg. per day orally for four days. On the fifth hospital day a sinus tachycardia developed with varying auriculoventricular block, bigeminal and trigeminal rhythm, and runs of Wenckebach periods. The serum potassium was 3.7 mEq. per L. at this time. The diagnosis of digitalis intoxication was made, the administration of digoxin was stopped, and supplementary potassium chloride given. The rhythm returned to normal. Throughout the hospital course whenever supplementary potassium was discontinued the serum potassium fell to low levels (3.2 mEq. per L.). Digitalis therapy was not reinstituted.

The diagnosis of myocardial infarction became doubtful when no serial changes occurred in the electrocardiogram and the white cell count and sedimentation rate continued at elevated levels. In addition the serum glutamic-oxalic transaminase rose from 80 units on day 2 to 345 units on day 20; the serum glutamic-pyruvic transaminase rose from 46 to 475 units in the same period. The alkaline phosphatase rose to 11.9 Bodansky units on day 24 and remained elevated. The reaction to the cephalin cholesterol flocculation test and serum bilirubin was always normal. Only one eosinophil was seen in ten differential blood counts.

On day 15 the diagnosis of diabetes mellitus was made because of the development of glycosuria and elevated fasting blood sugars (125 to 350 mg. per ml.). Treatment with 1 gm. of tolbutamide daily was initially satisfactory but six days later it was necessary to change to NPH insulin. An initial dose of 20 units per day was gradually increased to 50, with supplementary doses of regular insulin. Despite these measures the diabetes was difficult to control and glycosuria increased.

On day 20 anticoagulants were stopped because of the development of ecchymoses in the buttock area. Blood pressures in the range of 160 to 180 mm. Hg systolic and 110 to 120 mm. Hg diastolic were noted. Psychotic behavior with paranoid ideation developed. Control required large amounts of sedatives. A lumbar puncture did not reveal any abnormalities. Determinations of the urinary catecholamines and 5-hydroxyindolacetic acid were normal. On day 24 urine ketogenic steroids were 120 to 138 mg. per twenty-four hours (normal 6 to 20), and 17-ketosteroids were 38.5 mg. per twenty-four hours (normal

FIG. 1. Complete replacement of gallbladder wall by neoplasm is noted, with extension into the liver. The uninvolved common bile duct is visualized.

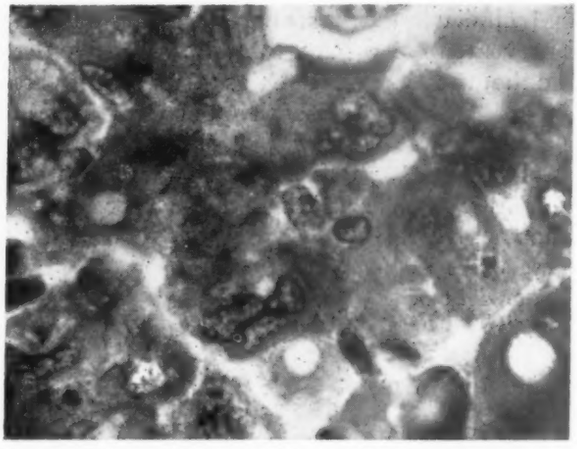

FIG. 2. A cluster of basophils in the pituitary is seen, with typical hyaline intracytoplasmic changes. Oil immersion; original magnification × 950.

6 to 15). A liver biopsy performed on day 37 revealed undifferentiated metastatic carcinoma.

Bullous pyoderma and apparent septicemia accompanied rapid clinical deterioration, with spiking temperatures, mental stupor, semicoma and hypotension. Supportive treatment with vasopressors and antibiotics was unsuccessful. The patient died on August 29, 1959, thirty-nine days after admission.

Autopsy was performed nine hours after death and included examination of the cranial cavity and spinal cord. On external examination the patient was an obese white woman appearing the stated age of sixty-two; she measured 5 feet 3½ inches and weighed 150 pounds. Coarse facial hair was present. No further pertinent findings were noted on inspection.

The body cavities contained no excess of free fluid. The liver protruded 8 cm. below the right costal margin and contained numerous coarse nodules measuring 4 to 5 cm. in diameter. An intrahepatic firm white mass 10 cm. in diameter was contiguous with the gallbladder. Several discrete and confluent nodules of similar tissue (presumably lymph nodes) were noted in the abdominal para-aortic area, around the head of the pancreas and near the free edge of the gastrohepatic ligament.

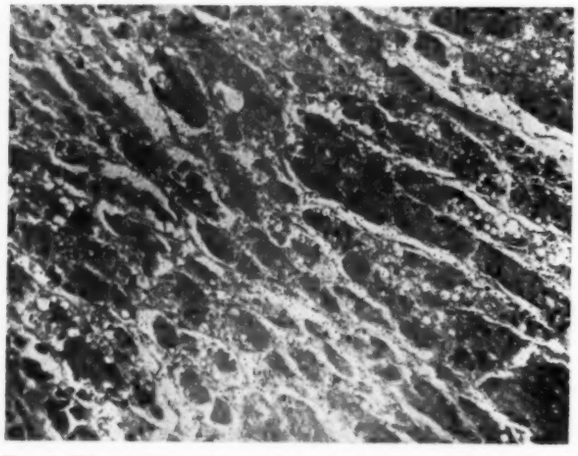

FIG. 3. The pattern of the cell cords in the zona fasciculata of the adrenal cortex is demonstrated. Varying degrees of vacuolization and individual cell size are conspicuous. Original magnification × 400.

The common bile duct was dissected from the ampulla of Vater and was patent into the smaller intrahepatic radicles. The cystic duct within 1 cm. of the junction with the common bile duct was replaced by firm white tissue which also replaced the remaining gallbladder wall and on the hepatic face infiltrated the liver. A small stone was partially lodged in the neck of the gallbladder. The heart weighed 370 gm. and the coronary arteries were markedly narrowed by non-occlusive arteriosclerosis, particularly the left anterior descending artery. The myocardium appeared normal. The lungs weighed 750 gm. (right), and 500 gm. (left) and exuded considerable fluid on cut section. Nodules varying from 2 to 5 mm. were noted on the pleural surface and in the parenchyma on cut section. The liver weighed 2,100 gm. and was normal except for the numerous nodules described, and a small calcified multiloculated 4 cm. cyst in the posterior right lobe. The spleen was normal. The pancreatic head was encased in the described "nodal" tissue which could be dissected from it with a plane of cleavage. Small areas of fat necrosis were discernible in the head and around the tail. The main duct was not dilated. The adrenals were normal in appearance. The remainder of the gross autopsy (kidneys, urinary bladder, genital organs, gastrointestinal tract, neck organs, brain and pituitary, spinal cord, vertebral column and great vessels) was within normal limits.

Microscopic examination revealed an undifferentiated carcinoma in the gallbladder, lymph nodes and liver. There was a necrotizing lobular pneu-

monitis and an unrelated echinococcal cyst of the liver, 4 by 4 cm. in diameter. Small foci of fat necrosis were present in the peripancreatic fat. The remaining organs were essentially normal, except for the pituitary and adrenals.

In the adrenals, the zona fasciculata was uniformly increased in size, with the zona glomerulosa represented only by compressed peripheral islands. The cords of the fasciculata were composed of a varying pattern of lipid-rich and lipid-poor cells. These changes, although non-specific, are somewhat unusual and have been seen in hypercorticoid states (spontaneous human and artificially produced animal cases). In the pituitary, various stains (hematoxylin and eosin, Wilson, periodic acid-Schiff, Heidenhain) revealed the large basophils with cytoplasmic hyaline changes, characteristic of Crooke's abnormality, generally focal in nature although occasionally diffuse. This abnormality was present in over half the basophils observed and, although more defined with the special stains, was readily seen in the routine hematoxylin and eosin stain.

The autopsy findings thus consisted essentially of an anaplastic carcinoma of the gallbladder with regional and distant metastases; an adrenal normal on gross examination but with histologic changes as described; and a pituitary showing characteristic basophil changes as observed in hyperadrenocorticoid states. (Fig. 1, 2 and 3.)

COMMENTS

Course of the Combined Disease. Characteristic of these cases is a rapid progression of the clinical course. Of the twenty-eight cases the briefest duration of illness was thirty-three days, the longest three years, the average nine months from first symptom to death. In twelve of the cases the patients lived five months or less. The course of Cushing's syndrome averages four and a half years or more [*1*]. The time from diagnosis to death in the present cases would be better compared to that expected in the associated neoplasm, however, which independently would have a worse prognosis. Both anaplastic carcinoma of the bronchus and pancreatic neoplasm may run a rapid course of three months or less [*42*]; the span in thymic carcinoma is more variable, but may also be short [*31,34*]. Therefore, no general prognostic remark is justified regarding the rapid course in cases of combined disease.

In individual cases, however, the rapid course of events, particularly the rapid evolution of the Cushing's syndrome itself, would seem noteworthy. Thorne [*4*] points out that, in comparison to Cushing's original cases "The coincidence of neoplasia materially changes the clinical picture . . . Such a poor prognosis is partially attributable to the coexistence of two serious diseases in the same patient but this should not be allowed to disguise the fact that the endocrine disorder itself ran a remarkably acute course."

Leyton [*13*] describes an eleven year old white girl in whom moon-face, hirsutism, abdominal swelling and thinning of the extremities were noted following an appendectomy. A diabetic-type glucose tolerance curve developed. Two and a half months after the onset, the patient died suddenly in convulsions. Autopsy revealed carcinoma of the thymus. The adrenals weighed 20.6 gm., prominent for an eleven year old subject.

The illness of a thirty-six year old man reported by Thorne [*4*] lasted six months and was first manifested by a gain in weight. The patient manifested the major clinical characteristics of Cushing's syndrome (plethora, easy bruising, trunkal obesity, striae, hypertension, osteoporosis) before death from oat cell carcinoma of the lung. Several urinary 17-ketosteroid excretion levels were elevated. The adrenals and pituitary were normal at autopsy.

Spaulding [*3*] describes a fifty-six year old white man whose entire course lasted thirty-three days; autopsy showed oat cell carcinoma of the lung with metastases to liver and both adrenals. Moderate clinical and marked laboratory evidence of the hyperadrenocortical state were seen.

The patient with carcinoma of the gallbladder described herein lived four months from the first symptom of chest pain to death in septicemia. Characteristic abnormalities of carbohydrate metabolism and steroid excretion were increasingly prominent during the last month of life.

The patient with the longest survival, three years, was a twenty-two year old girl described by Frank [*18*]. At age nineteen the patient noted a mass in the neck. This was biopsied and reported to be "Malpighian celled carcinoma." Three years later the very rapid onset of clinical Cushing's syndrome was observed and the patient died shortly thereafter. Autopsy disclosed a mediastinal thymic tumor with metastases to the hilar nodes.

Biochemical Abnormalities—Hypokalemic Alkalosis, Disturbance of Carbohydrate and Steroid Metabolism. Marked electrolyte abnormalities were common among these cases. On the evidence available,

hypokalemic alkalosis was present in at least ten of the twenty-eight cases [*3–6,9,10,14,20,25*, present case]. Rosenberg [*20*] discusses a forty year old white woman who died in two and a half months with metastatic carcinoma of the pancreas and full blown Cushing's syndrome. Serum potassium measured as low as 1.8 mEq. per L.; carbon dioxide was "greater than 34.7 mEq. per L."

A seventy-six year old woman with metastatic oat cell carcinoma of the lung, moon face, hirsutism and hypertension is described in "Case Records of the Massachusetts General Hospital" [*6*]. This patient lived seven weeks after her final illness started and during this period the carbon dioxide measured 40.7 mEq. per L., potassium 3 mEq. per L. and arterial pH 7.55.

Spaulding's patient [*3*], a fifty-six year old white man, was mentally obtunded with a carbon dioxide combining power of 114 volumes per cent and serum potassium of 10 mg. per cent. The blood pH was 7.7. The confusion cleared as the electrolyte balance was restored.

The sixty-two year old white woman described herein had serum potassium levels as low as 3.2 mEq. per L. and required potassium supplementation to counteract digitalis intoxication, produced by 2 mg. of digoxin over a four-day period. The serum carbon dioxide was 36.8 mEq. per L.

Carbohydrate metabolism was disturbed in almost every case, and when performed, diabetic-type glucose tolerance curves were the rule. Adequate control of the diabetic state was often difficult or impossible. A common course would find the patient originally non-diabetic, then manifesting hyperglycemia easily controlled by the usual measures, and finally in a state largely or completely resistant to huge doses of insulin.

Kovach and Kyle [*5*] mention, in their description of a twenty-two year old white man with Cushing's syndrome and bronchogenic carcinoma, that "insulin requirement, starting with 10 units of NPH iletin, rose rapidly to 35 units, but complete control of the diabetes was never obtained."

A sixty-four year old white woman described by Parsons and Rigby [*25*], with ovarian carcinoma, initially showed glycosuria shortly following operation for removal of the pelvic mass. The diabetes was first controlled with diet and the administration of 44 units of insulin daily, but management later became difficult. This patient, the only one with ovarian neoplasm in the series, typically displays most of the characteristics of this group of patients with combined hyperadrenocorticism and malignancy. The total course of illness, from first symptom of abdominal fullness to death, was four months. On physical examination and study, hypertension, plethera, hirsutism, mental changes, peripheral edema, poor wound healing, hypokalemic alkalosis and markedly elevated steroid levels were found. Autopsy disclosed widely metastatic anaplastic ovarian carcinoma with no suggestion of arrhenoblastoma or masculinovoblastoma. The adrenals weighed 26 gm. and the cortices were hyperplastic.

The patient with carcinoma of the gallbladder herein described, not previously diabetic, first exhibited elevated blood sugars twenty-four days before death (125 to 350 mg. per cent). Control with an oral hypoglycemic agent was satisfactory to start with but four days later NPH insulin was required instead. The initial dose of 20 units daily was gradually increased to 50 units, with supplementary regular insulin, and on this regimen glycosuria persisted.

Abnormalities of steroid excretion were common in this group of patients. Worthy of remark, however, are four patients with biochemical evidence of the hyperadrenocortical state but lacking clinical signs of Cushing's syndrome. A sixty-eight year old man is discussed in "Case Records of the Massachusetts General Hospital" [*9*]. Two and a half months prior to death an infiltrate was found on a chest roentgenogram, the first evidence of disease. Subsequently signs and symptoms of spinal compression fractures were noted and marked osteoporosis was described. The patient died of overwhelming infection. Postmortem examination revealed oat cell carcinoma of the lung with metastases to mediastinal modes, liver and vertebrae. The adrenals weighed 30 gm. and the cortices were diffusely hyperplastic. There were no adrenal metastases. The 17-OH corticosteroids measured 39 and 34 mg. per twenty-four hours and the 17-ketosteroids 23 and 17 mg. per twenty-four hours. No aldosterone was found in the urine.

Gold and Shnider's case [*10*] was a forty-eight year old white man whose illness ran a total course of six and a half months. The patient's first complaints were of cough and chest pain. An inoperable pulmonary neoplasm was found

at exploration and the patient died one month later of cardiac arrhythmia. Throughout his course no stigmas attributable to hyperadrenocorticism were apparent except possibly peripheral edema. Autopsy showed anaplastic carcinoma of the lung with widespread metastases, including the adrenals. Blood corticoids, urinary 17-ketosteroids and hydroxycorticoids were all elevated.

A forty-six year old white man whose total illness spanned two months is described by Metzler and Flink [*11*]. The signs and symptoms were all attributable to carcinoma of the lung and no physical evidence of Cushing's syndrome was found. Twenty-four hour urinary ketosteroid and 17-hydroxycorticoid levels were elevated. At autopsy a "small cell carcinoma" was found in the left mediastinum, again with widespread metastases. The adrenals weighed 25.5 gm., were not invaded, and the cortices were "somewhat prominent."

White's patient [*8*], a fifty-eight year old man, was well until eight weeks before death. He first noted pressing pain on the right side of the head, followed by symptoms of diabetes insipidus. Massive edema occurred and the patient died in shock after myocardial infarction. Again no clinical evidence of Cushing's syndrome was seen. Autopsy revealed anaplastic bronchogenic carcinoma with metastases to hilar nodes, liver, adrenals, cerebrum and posterior pituitary. There was adrenal cortical hyperplasia. The average daily 17-ketosteroid urine excretion was 30.5 mg. in a pooled six-day specimen.

The four cases in which steroid studies revealed hyperfunction of the adrenal cortex but which lacked clinical evidence thereof were fulminating. None of the patients lived more than six and a half months after the first symptoms. Possibly the rapid course did not allow time for the development of overt stigmas of Cushing's syndrome.

Which Occurs First? Hyperadrenocorticism or malignancy, which comes first? Study of these cases gives no final answer. In Frank's case [*18*] Malpighian celled carcinoma of the thymus was proved by biopsy three years before the sudden clinical onset of Cushing's syndrome. Of the six other cases of carcinoma of the thymus two were initiated by symptoms of Cushing's syndrome (typical obesity [*15*], facial hair, plethora [*14*]), one by cough caused by tumor [*13*], Case 2, and three by symptoms not specifically due to either disease.

Of the twelve cases of lung carcinoma the first evidence of disease in four was due to adrenocortical overactivity (weight gain [*4*], Cases 1 and 2, obesity [*12*], and hirsutism [*7*]). Five patients had initial evidence of disease caused by neoplasm (cough and chest pain in three [*5,10,11*], pain in head due to metastases [*8*], and abnormal chest roentgenogram [*9*]). In three cases the onset was indefinite.

In the five patients with pancreatic carcinoma, abdominal discomfort and vomiting presumably caused by neoplasm, initiated symptoms in one [*19*]; two first presented with evidence of Cushing's syndrome (round face [*20*], hirsutism [*14*]). The first symptoms in two patients were uncertain.

Typical fatty change of hyperadrenocorticism initiated the illness in a fourteen year old boy with sympathicoblastoma [*23*]. The first symptoms of illness in the cases of ovarian carcinoma [*24*], thyroid neoplasm [*24*] and the present case of gallbladder malignancy are not indicative of either type of disease.

There is no clear-cut evidence to suggest which of the two, malignancy or hyperadrenocorticism, comes first. The initiating mechanism of the syndrome of the combined diseases remains a conjecture. However, evidence is available revealing abnormal steroid excretion in patients with neoplasm. Studies in human patients with cancer have shown a significant increase in the urinary excretion of 11-hydroxyetiocholanolone [*33*]. Further, experimental animals bearing certain neoplasms have shown an increase in adrenal weight [*41*]. This relates to the particular animal and tumor, and may be a transient phenomenon. In general, it must be stated, no clear-cut pattern of abnormal steroid excretion has been demonstrated in patients with malignancies and no evidence exists which suggests that non-endocrine tumors can cause hyperadrenocorticism [*35*].

Were the hyperadrenocortical state to induce malignancy, patients with long-standing Cushing's syndrome would be likely candidates for the combined disease. This, however, is not the case [*1*], for no case of prolonged Cushing's disease later developing into carcinoma has been reported. The work of Whiteley and Green [*36*] points out the possibility, on the other hand, that cortisone may facilitate tumor growth. In rats and mice pretreated with cortisone before injection of tumor, the neoplasm grew far more successfully than in control animals. In one

instance, through this technic, human oat cell carcinoma was successfully transplanted to mice. Thus cortisone has been demonstrated to assist in the growth of heterologous (including human) neoplasms in laboratory animals [*36–38*]. Further, corticosteroids have stimulated the growth of certain autologous induced animal neoplasms [*39,40*]. This finding depends on the tumor type and on the dose:time administration of the steroid. Whether steroid stimulation of tumor is related to the altered humoral environment noted in animal and certain human neoplasms, or whether related more specifically to the altered host immune response, is unresolved. In general, altered corticosteroid metabolism can reasonably be considered a possibly significant factor in either the induction or progress of a particular neoplasm.

The possibility that adrenal metastases may somehow lead to hyperfunction of the adrenal cortex appears to be eliminated. Only five of these twenty-eight patients had metastases in the adrenals. Gold and Shnider [*10*] point out that "adrenal metastases seem an unlikely explanation of the Cushingoid state since 20 to 30 per cent of lung carcinoma show such metastases without functional abnormality of the adrenals."

SUMMARY

The significance of an association between non-endocrine neoplasms and the hyperadrenocortical state is established. A further case of the syndrome of the combined disease states is described, the first of carcinoma of the gallbladder to be noted in this connection.

The evolution of the combined disease and the remarkable biochemical abnormalities manifested are discussed.

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Mesothelioma Associated with Cryoglobulinemia*

Report of a Case

ARIF I. ÇETINGIL, M.D., MUHLIS A. ÖZEN, M.D. *and* ÖZKAN M. SANDALCI, M.D.
Istanbul, Turkey

CRYOGLOBULINEMIA is found in various pathologic states. Lerner and Watson [*1*], who introduced the term cryoglobulinemia, used it to designate the precipitation of serum proteins in the cold, with subsequent dissolution at body temperature. Lerner et al. [*2*] studied 121 cases, representing a variety of ailments, for the presence of cryoglobulinemia and found it present in thirty-one, whereas none was demonstrable in 40 control cases. Later, similar results were reported by others. Cryoglobulinemia occurs most frequently in cases of myeloma [*2–8*]. It has also been isolated in cases of lymphosarcoma [*9*], lymphatic leukemia [*10–13*], kala-azar [*14*], subacute bacterial endocarditis [*15*], periarteritis nodosa [*16*], rheumatoid arthritis [*17*], coronary artery disease [*18*], hepatic cirrhosis [*19,20*] and macroglobulinemia [*7*].

Cases of essential cryoglobulinemia, in which no other detectable disease is present, have been reported [*7,8,21–27*]. Recent studies [*7,8,22,23*] have led to a better understanding of the manifestations and physico-chemical properties of this protein.

The clinical manifestations of both essential and secondary cryoglobulinemia include sensitivity to cold, atypical Raynaud's phenomenon, purpura, stomatitis, bleeding from the nose and mouth, retinal hemorrhages, vascular stasis, mottling of the lower extremities, dyspnea, cyanosis, abdominal distress, diarrhea, melena, deafness, gangrene of the extremities, multiple arterial and venous occlusions involving many blood vessels, pulmonary vascular sclerosis, urticaria and ulceration of the skin [*7,22*].

The purpose of this report is to record the presence of cryoglobulinemia in a patient with mesothelioma, an association not yet listed in the literature.

CASE REPORT

M. A., a fifty-one year old man, was admitted to the Second Medical Clinic on April 17, 1959. His chief complaint was pallor and paresis, with subsequent cyanosis and numbness of the hands, feet, nose and ears on exposure to moderate cold. More recently pain in the posterior right side of the chest developed.

Five years before, when he had none of these complaints, dyspnea on exertion which lasted for three months developed and later disappeared. He was well until two years prior to admission when he experienced retrosternal pain on exertion, which cleared up after ten months. In the winter of 1958 he noticed that his nose, ears, hands and feet became pale and numb on exposure to the cold. After a short time they became bluish and began to tingle and throb. This condition disappeared during the summer but reappeared in the winter of 1959. He began to have pain in the right side of his chest fifteen days prior to admission. This pain was not severe. There was no cough or bloody expectoration.

Examination on admission revealed arcus senilis was present bilaterally; in the fundi venous distention, tortuosity, and thinning of the retinal arteries were revealed. The patient was edentulous. Pressure at the level of the sixth rib in the right axillary region was painful. The heart and chest were normal. The blood pressure was 124/70 mm. Hg. He appeared slightly cyanotic. There was no evidence of lymphadenopathy, hepatomegaly or splenomegaly. Bilateral inguinal hernia were present. Pulsations could not be felt in the dorsal pedis arteries or in the left posterior tibial artery. Dilated venules were observed on his face, nose, both lower legs and the dorsums of the feet. The veins were most prominent on the legs and feet. There were no other significant physical findings.

He was moderately obese and had suffered no loss of weight. His appetite and nourishment were normal. He had had no allergic reactions and there was no tendency to abnormal bleeding. In short, he did not have the appearance of an acutely ill patient. It was

* From the Second Medical Clinic of the University of Istanbul, Turkey. Manuscript received July 5, 1960.

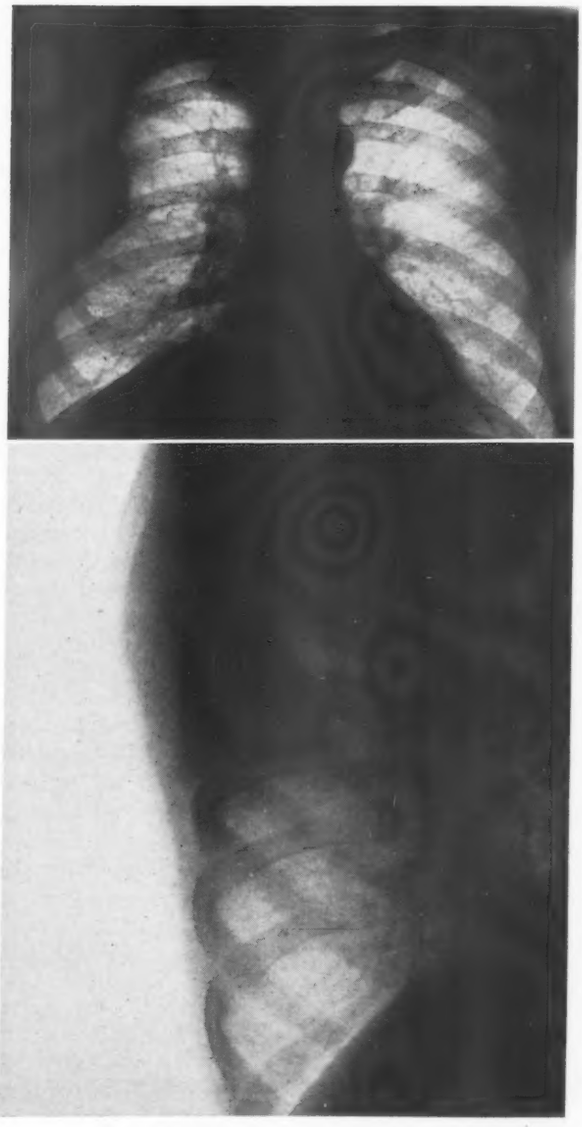

FIG. 1. *Top*, posteroanterior roentgenogram of the chest. *Bottom*, right oblique roentgenogram of the chest.

the Raynaud-like symptoms, for which the patient was hospitalized, that led to the investigation for cryoglobulinemia. When the clinical suspicion of cyroglobulinemia was verified, it was necessary to determine whether the cryoglobulinemia was primary or secondary.

The blood cell counts (red, white) and hemoglobin were normal. The hematocrit was 52 per cent. The urine findings were within the normal range, specific gravity 1.022, and an acid reaction; no proteinuria, Bence-Jones proteins or glycosuria was observed. Results of serologic tests for syphilis were negative. The erythrocyte sedimentation rate (Westergren) was 6 mm. in one hour at room temperature, 18 mm. in one hour at 37°C. and 42 mm. in one hour at plus 4°C. Examination of the bone marrow revealed no

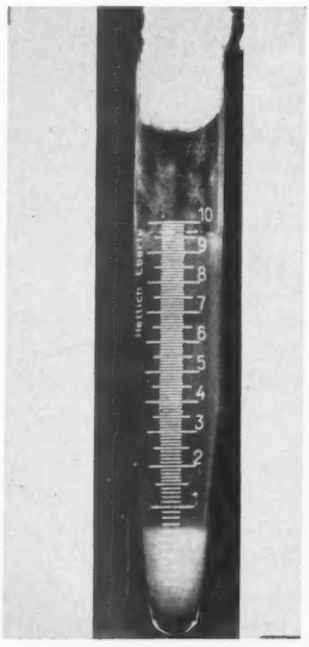

FIG. 2. Cryoglobulin precipitated at the bottom of the tube is shown.

unusual findings and the number and morphology of the plasma cells was normal. Fasting blood sugar, blood urea, serum calcium, phosphorus, acid phosphatase (Bodansky), cholesterol and uric acid levels, and the Kunkel-phenol and Congo red tests were within normal limits. The serum total proteins (Kjeldahl) were 7.8 gm. per cent, albumin 5 gm. per cent and globulin 2.8 gm. per cent. After cryoglobulin extraction the serum globulin was 2.1 gm. per cent. The formol gel reaction was negative. The cold agglutinin titer was 1:2048 at plus 4°C. When this test was repeated, it was again found to be strongly positive (1:2048). A Coombs' test had negative results. Blood smears were extremely difficult to prepare as the erythrocytes tended to form clusters. The electrocardiogram was within normal.

On roentgenographic examination of the chest a triangular density was found in the right side of the lung about the level of the sixth rib. (Fig. 1.) Two different pleural punctures were attempted, as the density was thought to be in the pleura, but no fluid could be located. Microscopic examination of the material aspirated revealed spindle cells which were uniform in structure. Mitosis was not recognized. The pathologic diagnosis was mesothelial tumor.

In the literature on cryoglobulinemia many variations in physicochemical properties are described. We have tried to compare some of the previous findings in the literature with our own [*22,23*].

METHODS

Ten milliliters of serum, separated from the blood immediately upon withdrawal from the patient, was

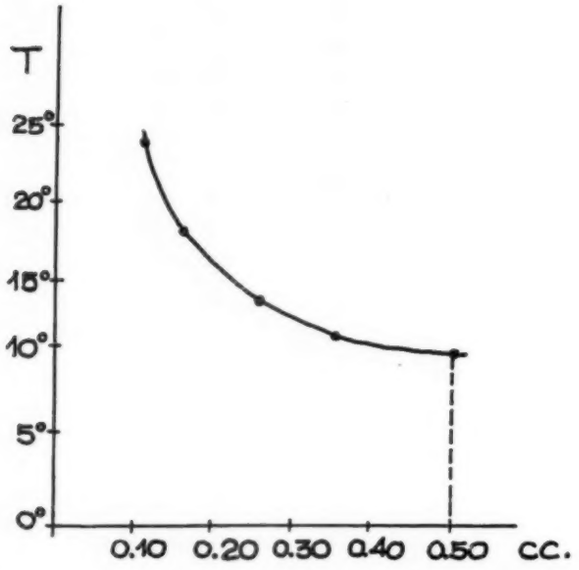

FIG. 3. The degree of the commencement of precipitation and maximum point in gradually refrigerated serum is shown.

put into a graduated test tube and kept for twenty-four hours at 4°C.; 0.5 cc. of precipitate collected at the bottom of the tube. (Fig. 2.) After one month of storage at 4°C. there was no change in the amount.

The precipitates that had been kept twenty-four hours and one month, respectively, dissolved when heated to 37°C. The same amount of material was reprecipitated when these serums were refrigerated at 4°C. The solidity of the precipitate kept at 4°C. for one month increased. On heating it dissolved in three minutes. The precipitate which formed when the serum was refrigerated again at 4°C., was dissolved again at 37°C. and then reprecipitated at 4°C. This process of reprecipitation was carried out six times without a change in the amount of precipitate formed.

When the serum was heated to 56°C. for half an hour, subsequent refrigeration at 4°C. produced the same amount of precipitate as the unheated serum; this precipitate dissolved again when heated to 37°C. and reappeared in the same amount on refrigeration.

One milliliter each of heparinized plasma, oxalated plasma and serum were put into Lee-White coagulation tubes and kept for one day at 4°C. In each of the three tubes a precipitate formed in equal amounts. When the three tubes were kept in the refrigerator for one week, no change occurred in the amount of precipitated protein.

Serum was gradually refrigerated in a graduated tube and the starting point of precipitation and the amount of precipitate were observed. Precipitation began at 24°C., reached a maximum at 10°C., and did not change when refrigerated to 4°C. (Fig. 3.)

The effect of the concentration of cold-precipitable protein on the temperature decrease required to start precipitation was studied by diluting the patient's serum with normal saline solution. Precipitation began to decrease gradually at a temperature of 24°C. in the undiluted serum and 18°C. in 1:5 dilutions. (Fig. 4.)

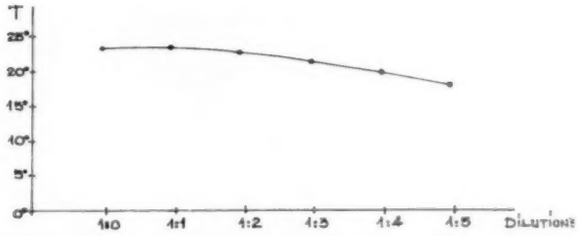

FIG. 4. Effect of dilution by normal saline solution on the degree at which precipitation started in the serum.

Results of the Sia test in serum were markedly positive. After cryoglobulin extraction they were negative. Although this test was repeated many times the results were always the same. Pyroglobulin was absent from the serum.

The coagulation mechanisms of the patient were studied. The bleeding time, clotting time, clot retraction time, capillary fragility test, platelet counts, prothrombin time thromboplastin generation test (Douglas and Biggs) were all within normal limits. After extraction of cryoglobulin the prothrombin time and thromboplastin generation test were unchanged.

The fibrinogen level of the plasma was found to be 340 mg. per cent. After the cryoglobulin was extracted the fibrinogen level was 300 mg. per cent. This small difference was thought to be due to some fibrinogen adsorption by the cryoglobulin. To verify that there was no striking loss of fibrinogen, as had occurred in one case [*23*], 10 ml. of normal saline solution was placed in each of two test tubes, and in one of them 0.5 ml. of the patient's whole plasma was added while to the other was added 0.5 ml. of plasma from which the cryoglobulins had been extracted. Three drops of topical thrombin (10 units per ml.) were then added to each tube. No significant difference was observed in the volume of the fibrin clots produced in each tube.

Paper electrophoresis (Whatman No. 1 paper, veronal buffer pH 8.6 and ionic strength of 0.05, bromphenol blue stain) was performed with whole serum, saline-washed cryoglobulins precipitated at 4°C. and residual serum after the cryoglobulin had been extracted. The cryoglobulins were observed to migrate to the region of the gamma globulin. (Fig. 5.)

COMMENTS

Both essential and secondary cryoglobulinemia are observed more often in patients in the sixth or seventh decades; 75 per cent of the cases reported fall in this group [*22*]. The oldest patient recorded was eighty-five years of age [*24*].

The physicochemical properties of cryoglobulinemia differ in each case. In our case the results of some of the studies made parallel those of Volpe et al. [*22*]. In their case, however, the cryoglobulin refrigerated for one month formed a firmer gel than fresh cryoglobulin, and the cryoglobulin refrigerated at 3°C. for a few weeks dissolved only to the extent of 70 to 80 per cent in forty-eight hours when brought to 37°C. In our case the precipitate dissolved completely in three minutes. In their experiments there was a gradual decrease in the amount of cold-precipitable protein of the serum which was refrigerated repeatedly at 3°C. and heated to 37°C. After five to fifteen repetitions the precipitate disappeared. There was a gradual decrease in the cold-precipitable proteins in serum kept at room temperature for a long time. This process took place more rapidly in serum kept at 37°C. for three weeks. In our case, serum kept twenty-four hours or one month at 4°C. dissolved at 37°C. When it was refrigerated again to 4°C. the same amount of precipitation occurred. Although this process of heating and refrigerating was repeated six times, the same quantity of precipitate was recovered each time. There was no decrease in amount of precipitate when the serum was left at room temperature for one month. In the case reported by Volpe et al. the cold precipitate disappeared completely or almost completely when the patient's serum was heated to 56°C. for thirty minutes. We were unable to demonstrate such a decrease even though the experiment was repeated several times. When the temperature of the serum was lowered progressively, Volpe et al. noted that precipitation began at 28°C. and the amount of cryoglobulin increased almost linearly. Precipitation in our case commenced at 24°C., giving the appearance of flocculations within the serum. The maximum precipitation was 0.5 ml. at 10°C. and although refrigeration was continued down to 4°C., the amount of precipitate was unchanged. (Our estimates were based on volumes whereas Volpe et al. expressed theirs in grams.) In another recorded case precipitation started at 31°C. [*23*]. In both our case and Firkin's [*23*] the same amount of cold-precipitable protein was obtained in oxalated and heparinized plasma and in the serum. Volpe et al. found that the precipitable protein in both the refrigerated serum and the heparinized plasma diminished and disappeared in two weeks.

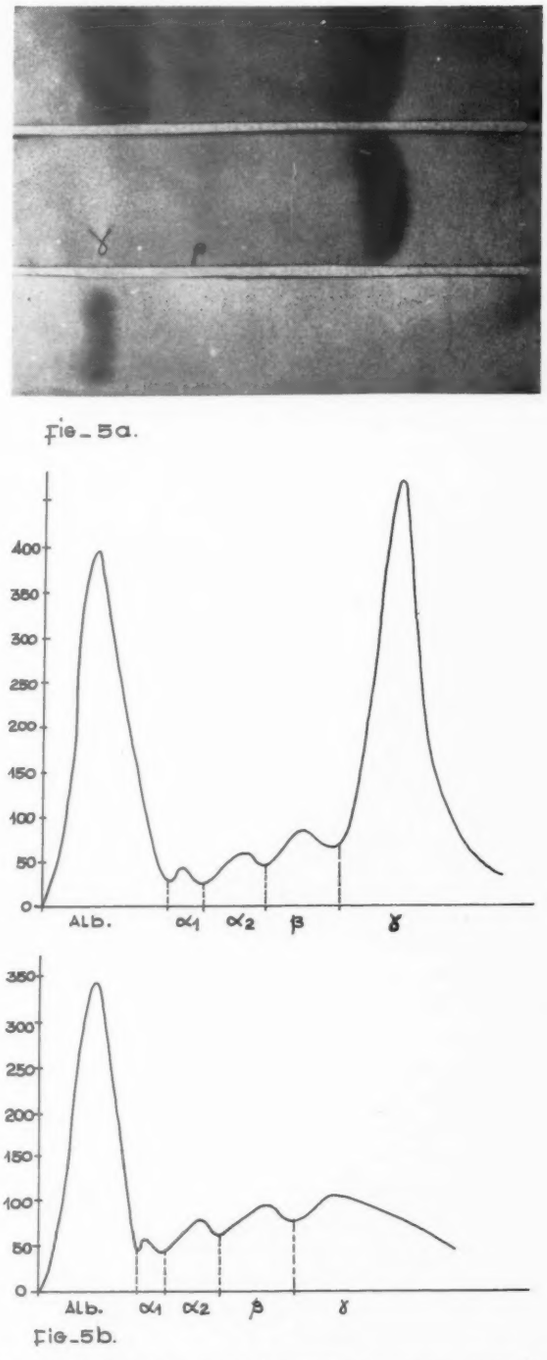

FIG. 5. Electrophoresis of the patient's serum dyed by bromphenol blue. A, electrophoresis of the whole serum (*top*); serum from which cryoglobulins were extracted (*middle*); and precipitated, saline-washed cryoglobulins (*bottom*). B, paper electrochromatogram made from the patient's whole serum (*top*); and serum from which cryoglobulins were extracted (*bottom*).

Volpe et al. suggest, on the basis of their studies, that an immunologic process plays a part in the low solubility of this protein, which

affects some or all of the gamma globulin and probably requires the presence of complement. They cite as evidence for this the loss of cold precipitability of the serum heated for half an hour at 56°C., which they attribute to inactivation of heat-labile substances or to dissociation of the protein complex by heating. They offer as further evidence the inhibitory action of heparin on the precipitation of the protein. The negative results in our case indicate that the low solubility of the cryoglobulin could not be explained by an immunologic process. When the patient's serum was diluted in normal saline solution, as in their case, there was no significant change in the onset of precipitation until a 1:5 dilution was made, and then precipitation started at 10°C. rather than at 24°C.

All of these experiments demonstrate variations in the physicochemical properties of this abnormal protein in different cases [*7*]. It is probable that these variations in physicochemical properties in each case play a part in the variability of the numerous symptoms attributed to cryoglobulinemia. In our case, in addition to the cold-precipitable protein, cold agglutinins were present in high titer. Schwartz and Jager [*13*] had observed for the first time the presence of cold agglutinins in very high titer in association with cryoglobulins in a case of lymphatic leukemia. Later Rørvik [*28*] found cryoglobulinemia together with cold agglutinins in a case of multiple myeloma. Gaddy and Powell [*24*] reported that cold agglutinins were associated with essential cryoglobulinemia in a patient with Raynauds syndrome. In these three cases and in our case, there were no signs of hemolysis. Conn [*25*] reported on a patient with essential cryoglobulinemia associated with cold agglutinins in high titer and showing acute hemolytic anemia. In a case of chronic lymphatic leukemia with cryoglobulinemia and autoimmune hemolytic disease cold agglutinins were not present [*10*].

No abnormalities were found in the blood coagulation mechanisms of our patient before or after the cryoglobulin was extracted from the plasma and serum. Fibrinogen was not adsorbed very much onto cryoglobulin, as reported in another case [*23*].

In many cases of cryoglobulinemia an increase in plasmocytes in the bone marrow has been observed. It is for this reason that plasmocytes have been accepted as the source of cryoglobulins. On the other hand, several cases, such as ours, have been reported in which the bone marrow plasmocytes were not increased [*1,9,13,19, 22–24*]. In one instance [*23*] the bone marrow plasmocyte count was normal but the plasmocytes showed vacuolization. These findings suggest that plasma cells are not the source of the abnormal protein in every case. In our case the atypical mesothelial cells might possibly be considered the source of the abnormal protein; this is only a speculation.

The Sia test was repeatedly found to be markedly positive in our case. Although known to be a screening test for macroglobulinemia, the Sia test is not completely dependable [*7,29,30*]. The positive Sia test obtained in our case was apparently due to the cryoglobulinemia [*7,23*].

The erythrocyte sedimentation rate in our case was normal at room temperature, slightly elevated at 37°C. and definitely increased at 4°C. The sedimentation rate in plasma containing cold agglutinins is increased at 4°C. because of agglutination of the erythrocytes, but cryoglobulins lower the sedimentation rate when the precipitate is formed in the cold [*29*]. The reverse happens at 37°C. when the sedimentation rate is lowered in plasma containing cold agglutinins and increased in plasma containing cryoglobulins. As both cold agglutinins and cryoglobulin were present in our case, the sedimentation rate was found to be increased both at 37°C. and at 4°C. more at the latter temperature. The effect of cryoglobulins on the erythrocyte sedimentation rate at room temperature depends on its soluble properties; if it is readily soluble the sedimentation rate will be increased [*31*]. The absence of a markedly increased sedimentation rate at room temperature, anemia, lymphocytes, enlargement of lymph nodes, changes in bone marrow, and gel formation in the serum makes the possibility of a macroglobulinemia in our case unlikely.

Another interesting aspect of our case is the association of cryoglobulinemia and cold agglutinins with a mesothelioma. Mesotheliomas may be classified as follows [*32*]: (1) Diffuse mesothelioma, in which neoplastic mesothelial cells cover the entire pleural surface; and (2) localized pleural or solitary pleural mesothelioma, which is localized and well limited. The diffuse type consists of two components [*32,33*], epithelial and fibroblastic cells. The latter cells give the appearance of sarcomatous elements: Localized (fibrous) mesothelioma can either be benign or malignant. It is made up of fibroma

or fibrosarcoma cells. The benign type is uniform, without prominent mitoses, and is made up of spindle (fibroblast-like) cells. The malignant type is not uniform, exhibits many mitoses, and consists of spindle cells. Stout and Murray [*34*] reported that normal mesothelial tissue can acquire characteristics of fibrous tissue in tissue cultures. A solitary pleural tumor with fibrosarcomatous-type cells may grow in tissue culture like the epithelial cells characteristic of diffuse mesotheliomas. The conclusion reached is that both diffuse and solitary types are of mesothelial origin.

In our case the chief complaint was symptoms suggesting Raynaud's syndrome. In cases in which cryoglobulinemia and cold agglutinins are associated, the question arises as to which one causes the peripheral vascular symptoms. As Gaddy and Powell emphasized [*24*], this is very difficult. Since cryoglobulinemia is encountered frequently in cases with Raynaud-like symptoms, it may be concluded that the cryoglobulins played a part in the peripheral vascular symptoms.

Our patient was treated with prednisone in daily doses of 20 mg. for a period of two months, but no result was achieved.

SUMMARY

A case of mesothelioma associated with cryoglobulinemia and a high titer of cold agglutinins is presented.

The chief complaints were suggestive of Raynaud's syndrome and because of this the possibility of cryoglobulinemia or cold agglutinins was investigated, and both were found.

A mesothelioma was also detected coincidentally, the first reported case of such are association.

Some of the physicochemical properties of the cryoglobulin in this case are described.

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The "Stiff-Man" Syndrome and Hyperthyroidism*

EMILE E. WERK, JR., M.D., LEON J. SHOLITON, M.D. *and* RICHARD T. MARNELL, M.D.†
Cincinnati, Ohio

IN 1956 Moersch and Woltman described fourteen cases of "progressive, fluctuating, muscular rigidity and spasms" of unknown etiology and termed the condition the "stiff-man" syndrome [*1*]. Since then several additional cases have been reported or referred to [*2–8*], although it is unclear whether or not all of these constitute the same syndrome.

The case reported herein is unusual in that the stiff-man syndrome was associated with hyperthyroidism, an association not previously recorded although extensive muscular rigidity and myoclonic spasms have been described (rarely) in combination with Graves' disease. In this case, there was an improvement in the stiff-man syndrome following treatment of hyperthyroidism. Certain theoretic etiologic factors common to both the stiff-man syndrome and hyperthyroidism are suggested by this case.

CASE REPORT

P. V., a forty-four year old married Negro man, was admitted to the Cincinnati General Hospital on October 11, 1953, with the chief complaints of stiffness and weakness of muscles and difficulty in swallowing. Three months prior to admission the patient had "trouble getting food down, and a fullness with eating." With progression of these symptoms he became unable to ingest solids and eventually restricted his diet to soft and liquid foods. His appetite deteriorated and he had intermittent vomiting. He noted palpitation, excessive sweating, nervousness, intolerance to heat, weakness, and thickening of the skin over both anterior tibias. A 35 pound weight loss ensued. Two months before admission he had stiffness and aching involving the muscles of the neck, abdomen, chest, back and extremities; the weakness progressed. The right hip and both lower extremities were particularly affected and walking became difficult. The patient experienced severe intermittent cramping pains in the muscles. He described these as "spasms" or "muscle jerks" which took his breath away. He stopped working one and a half months prior to admission and remained at home in bed during most of that interval. When questioned, the patient also stated that in 1951 he had experienced episodes of palpitation, nervousness and a gradual weight loss of 30 pounds. The symptoms improved spontaneously and he regained his lost weight.

While in the army from 1943 to 1945 he was hospitalized briefly for "nervous headaches." He had been employed as a bartender for five years and previously as a bakery and factory worker. Alcoholic ingestion was minimal. There was no family history of goiter, hyperthyroidism or neuromuscular disorder.

On examination the pulse rate was 104 per minute, temperature 99°F., blood pressure 130/70 mm. Hg, respirations 16, and weight 138 pounds. The patient was a well developed Negro man with evidence of moderate weight loss. He was lying quietly in bed; the back and neck were maintained in a stiff position and it was an obvious effort for him to move. He was alert, oriented and responded appropriately to questions and commands. The skin was warm, soft and moist. Over the lower third of the anterior part of the legs the skin was thickened, with bluish brown "orange peel" markings and raised yellowish white boggy nodules. A 1-plus brawny edema of both ankles was present. Body hair was normal.

The head, ears, nose and throat were within normal limits. The pupils reacted well to light and accommodation. The extraocular movements and visual fields were intact. The fundi appeared normal. A bilateral lid lag was present. There was no gross exophthalmos. A generalized shotty lymphadenopathy was present. The thyroid was slightly enlarged, with an estimated weight of 35 gm. Respiratory movement was reduced although the lungs were normal to percussion and auscultation. The heart was not enlarged to percussion. There was a forceful apical and precordial pulsation, and a grade 2 systolic murmur was audible over the apex and pulmonic area. No abnormal masses or organs were palpated. The genitalia and rectum were normal.

* From the Department of Medicine, Veterans Administration Hospital and the University of Cincinnati College of Medicine, Cincinnati, Ohio. Manuscript received July 14, 1960.
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TABLE I

"STIFF-MAN" SYNDROME AND RELATION TO THYROID FUNCTION, PATIENT P. V., 1953–1960

Date	Neuromuscular Manifestations	Clinical Thyroid Status	Basal Metabolic Rate	Radio-iodine Uptake (% 24 hr).	Serum Protein-Bound Iodine (μg./100 ml.)	Treatment
October to December 1953	Marked rigidity; frequent, severe myoclonic spasms	Hyperthyroid	+43, +75 +73	100	...	10 mc. I^{131}
January to February 1954	Marked rigidity; occasional myoclonic spasm	Mildly hyperthyroid	+7, +5	...	...	...
February to April 1954	Marked rigidity; frequent, severe myoclonic spasm; ?grand mal convulsion	Hyperthyroid	+42	73	7	8 mc. I^{131}
May to December 1954	Rigidity slightly less; occasional myoclonic spasm	Euthyroid	...	78, 64	...	...
January 1955 to February 1957	Gradual lessening of rigidity; rare myoclonic spasm	Euthyroid	−19	46	...	...
March to June 1957	No change	Hypothyroid	−26	27	1.2	...
July 1957 to May 1960	Hypertonicity of spine still present; rare, mild myoclonic spasm	Euthyroid	−2	...	...	Desiccated thyroid, 3 gr. daily

The over-all appearance of the muscular system was strikingly similar to that of a patient with tetanus. The larger muscles appeared prominent and in a state of sustained contraction. The neck was fixed in a slightly flexed position. There was a marked lordosis of the back. The muscles of the neck, back, chest, abdomen and proximal extremities were rigid and resistant to passive movement. The upper extremities were usually held in a semi-flexed position. The lower extremities were extended and the right thigh could be flexed only minimally. There was no hypertonicity of the muscles of the face and hands, and the patient was able to relax his grip normally. Despite the muscular prominence due to the hypertonicity, there was atrophy and loss of muscle mass, most prominent in the shoulders and pelvic girdles and proximal extremities. There appeared to be generalized weakness, although it was difficult to measure in the face of the rigidity. It was a marked effort for the patient to push himself up to a sitting position. When he did so the back, neck and abdomen remained very stiff. Walking was accomplished with extreme difficulty. The entire trunk was stooped forward and the back was hyperextended and rigid. The gait was broad-based with a slight sway and dragging of the right side. While lying in bed the patient exhibited occasional myoclonic jerking movements of the shoulders and trunk in an extensor direction and flexing movements of the arms. The cranial nerves were intact. Sensory modalities were normal. The abdominal and cremasteric reflexes were hypoactive. The deep tendon reflexes were hyperactive. Unsustained ankle and knee clonus could be induced. No Babinski or Hoffman reflex was elicited. An outline of the patient's subsequent changes in neuromuscular manifestations and thyroid status is presented in Table I and photographs are shown in Figures 1 and 2.

During the first several weeks of hospitalization the intermittent attacks of painful muscular spasms and jerking became more frequent and intense, occurring repeatedly during each day. They were precipitated by palpating or tapping the patient's muscles, by procedures such as venepuncture, and during visits with friends or relatives. Severe episodes were brought on by a lumbar puncture, and muscle and skin biopsies. These were accompanied by a tachycardia up to 160 per minute, hyerptension of 190/120 mm. Hg, profuse sweating and hyperventilation. Spasms were lessened slightly by the administration of Demerol® and barbiturates. The sustained muscular hypertonicity described on examination at the time of admission persisted between the intermittent episodes. The dysphagia subsided.

A diagnosis of hyperthyroidism with localized pretibial myxedema was made and was confirmed by an elevated radioactive iodine uptake of 100 per cent,

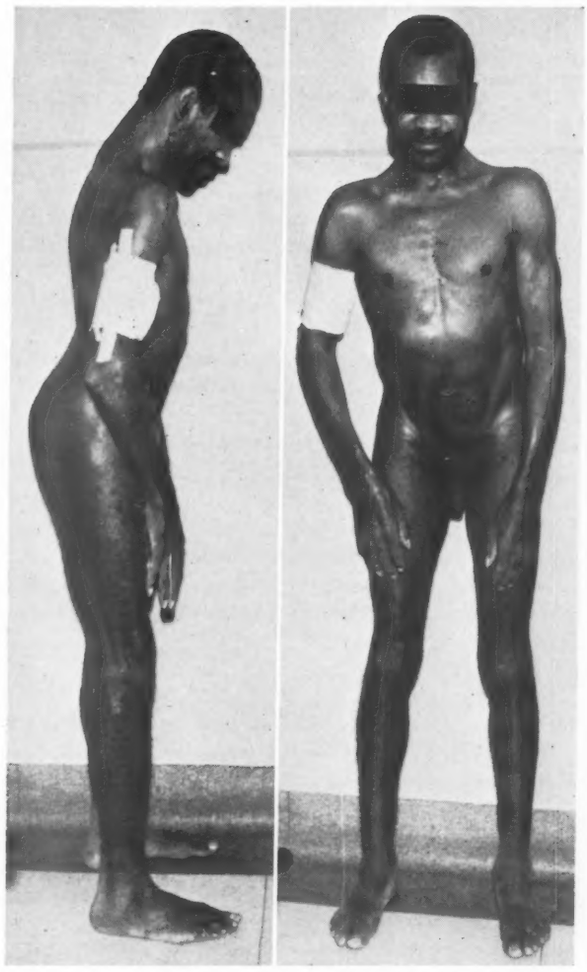

FIG. 1. Patient P. V. in March 1954 with the stiff-man syndrome and hyperthyroidism.

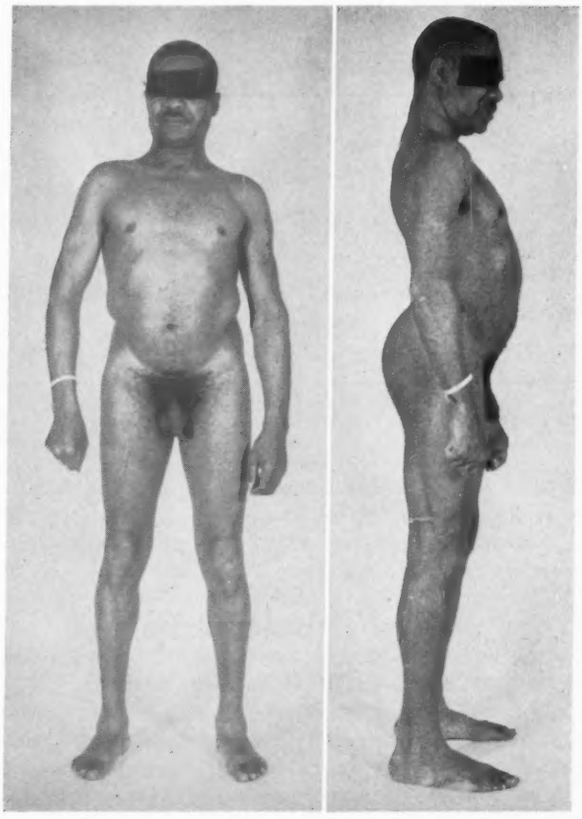

FIG. 2. Patient P. V. in February 1960. Myoclonic spasms and rigidity decreased. Hypertonicity of neck and back muscles with lordosis persists. Patient is euthyroid on a regimen of desiccated thyroid, 3 gr. daily, meprobamate and Dilantin.

a basal metabolic rate of plus 75 per cent and a pretibial biopsy specimen of the skin showing myxedema. However, the unusual neuromuscular disorder remained an enigma. A biopsy specimen from the right biceps muscle revealed only mild focal atrophy.

In November 1953 10 mc. of I^{131} were administered as treatment for the hyperthyroidism. The signs of thyrotoxicity gradually diminished during December and January. Concurrently, the muscular spasms became less frequent but still occurred. The patient walked very little, but he was able to use a wheelchair. It was suspected that the neuromuscular disorder might be related to psychogenic factors and the patient was transferred to a special medical-psychosomatic study ward where he remained until July 1954. Intensive psychiatric investigation was conducted during this period and is summarized subsequently. In brief, it might be stated that a psychogenic cause and effect sequence could not be demonstrated, but it was thought that the personality difficulties displayed by the patient were interrelated with the neuromuscular disorder.

In February 1954 there was a recrudescence of thyrotoxicity with increased sweating, nervousness and tachycardia. The thyroid gland was barely palpable. A basal metabolic rate was plus 42 per cent, radioactive iodine uptake 73 per cent, and a serum protein-bound iodine 7 μg. per 100 ml. An exacerbation of the myoclonic seizures developed. During attacks the patient often groaned and shouted complaints of pain and requested "shots" for relief. In March he received 8 mc. of I^{131}. In April a decrease of the sweating and tachycardia was once more observed and concurrently the myoclonic seizures were ameliorated. However, an occasional severe attack occurred, one of which suggested a grand mal convulsion. An electroencephalogram showed a diffuse fast dysrhythmia. Maintenance therapy with Dilantin® and phenobarbital was initiated. During May and June the patient was considered euthyroid. The myoclonic attacks were minimal. The sustained rigidity lessened sufficiently in the extremities to permit some walking, although the muscles of the neck, back, chest and abdomen remained hypertonic. There was no over-all

TABLE II
INSULIN TOLERANCE TESTS ON PATIENT P. V.
(0.1 μ/KG. GLUCAGON-FREE INSULIN)*

Data	Control	Minutes After Insulin				
		30	60	90	120	180
November 1953						
Blood glucose (mg. %).....	86	56	60	68	73	76
Serum phosphorous (mg. %)..	3.82	3.11	2.65	3.26	3.35	3.69
November 1954						
Blood glucose (mg. %).....	80	34	49	60	70	70
Serum phosphorous (mg. %)..	3.08	2.34	2.31	2.77	2.93	2.93

* The glucagon-free insulin was kindly supplied by Dr. W. R. Kirtley, Eli Lilly & Co.

weight gain since admission. In July 1954 the patient was discharged from the hospital.

During the next four months the patient had difficulty in taking care of himself at home alone, and in November 1954 he was admitted to the Cincinnati Veterans Hospital. The physical examination on admission revealed little change from his condition four months previously. He appeared euthyroid but had failed to gain weight and strength. The thyroid gland was slightly enlarged. The lesions of localized myxedema had regressed leaving smaller, dry scaly areas. The rigidity was prominent in the muscles of the abdomen, chest, back and neck. He could walk only with difficulty. During sleep the muscles were noted to be more relaxed but not normally so. The deep tendon reflexes were normal. The administration of phenobarbital and Dilantin was continued and the patient received physiotherapy. Further improvement progressed slowly. By June 1955 he was able to walk with the use of a cane; he was discharged from the hospital.

Since 1955 until the present (Fig. 2) he has been followed intermittently at the Veterans Hospital. The myoclonic spasms subsided almost completely except for an occasional mild jerking. The rigidity in the extremities is minimal and he walks freely with the use of a cane, climbs stairs and drives a car. His strength has improved considerably and he has gained 30 pounds. However, the hypertonicity and hyperextension in his spine have persisted. In May 1957 the patient appeared overtly hypothyroid. He was apathetic and complained of drowsiness. His pulse was 68, basal metabolic rate minus 26 per cent, radioactive iodine uptake 27 per cent and serum protein-bound iodine 1.2 μg. per 100 ml. He was treated with desiccated thyroid in doses up to 3 gr. per day and became euthyroid. The muscular spasticity showed no alteration with these fluctuations of thyroid activity. In an attempt to relieve the rigidity during the course of his attendance at the Veterans Hospital numerous other drugs were tried without success, including cortisone acetate, desoxycorticosterone acetate, tri-iodothyronine, Meratran,® reserpine and magnesium sulfate. Potassium chloride intensified the stiffness subjectively. The patient has refused a repeat muscle biopsy.

He is currently taking meprobamate and Dilantin which he believes helps the stiffness subjectively. Attempts to withdraw these drugs have resulted in painful increases of the muscular stiffness.

Laboratory Findings and Special Tests. Results of the following studies were repeatedly within normal limits: blood hemoglobin concentration, red blood cell count, white blood cell and differential count, blood urea nitrogen, serologic tests for syphilis, serum sodium, potassium, calcium, phosphorus, alkaline phosphatase, chloride, carbon dioxide content, total lipids, bilirubin, liver flocculation tests, routine urinalysis and electrocardiograms. In 1953 at the time of the initial hospital admission, the twenty-four hour urinary excretion of creatine was 0, creatinine 1.22 gm., nitrogen 13.7 gm. and calcium 136 mg. while the patient was receiving a low calcium diet. The urinary 17-ketosteroids were 5, 5.3 and 7.1 mg. per twenty-four hours. A result of the Robinson-Kepler-Power water test was normal. An eosinophil count was 88 per cu. mm. and four hours after the administration of 25 mg. ACTH decreased to 12 per cu. mm. The Watson-Schwartz test for urinary porphobilinogen had negative results. The cerebral spinal fluid protein, chloride and sugar concentrations were within normal limits.

Roentgenograms of the spine have repeatedly demonstrated a scoliosis to the right, a lumbosacral lordosis and loss of neck curvature. Roentgenograms of the skull, shoulders, pelvis, extremities, chest and gastrointestinal tract have revealed no abnormalities.

Results of oral glucose tolerance tests were normal in 1953 and 1960. Repeated urine tests have had negative results for reducing substances. Insulin tolerance tests with blood glucose and serum phosphorus determinations (Table II) were performed in 1953 (by Dr. Thomas Skillman) and in 1954. The blood glucose fall in the first test was decreased, as often observed in ill patients. The decreases in serum phosphorous concentration were normal in both tests.

Electromyograms were performed in 1955, alone and in conjunction with the special tests to be listed in the next paragraphs. Tracings obtained from various hypertonic muscles, while the patient was lying quietly, demonstrated normal rapid electrical discharges. (Fig. 3.) An increase in the activity was observed when a spasm was provoked similar to that shown in Figure 4A.

Response to succinylcholine chloride: An 0.1 per cent solution of succinylcholine chloride was administered as a continuous intravenous infusion at rates varying from 2.5 to 6.3 mg. per minute. During the slower rate the patient was more relaxed than usual and voluntary movement was still intact. Spasms could still be produced by tapping the muscles. (Fig. 4A.) With increasing rate of infusion, relaxation became more

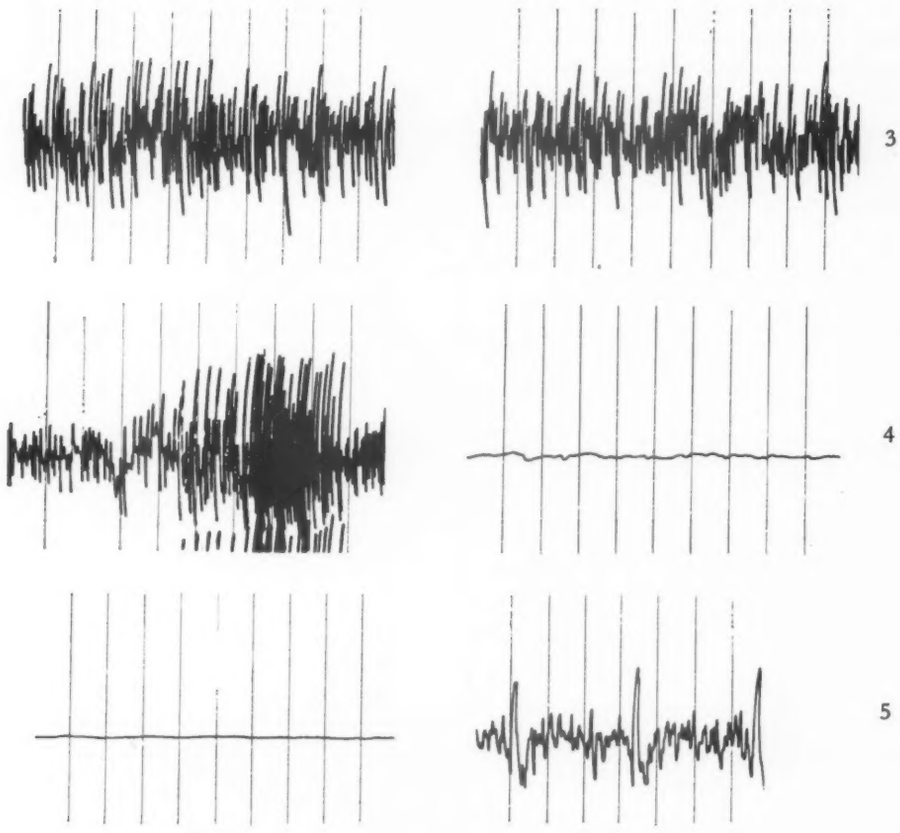

FIG. 3. Electromyogram 1955. Paper speed 30 mm. per second, skin electrodes, patient lying quietly. A, left flank, B, back.

FIG. 4. Electromyograms, right biceps, during succinylcholine chloride infusion (1955). A, infusion rate 2.5 mg. per minute, slight relaxation. A mild spasm could still be produced by tapping the patient, depicted by the increase in activity. B, infusion rate 6.3 mg. per minute, complete relaxation.

FIG. 5. Electromyograms during spinal anesthesia with complete bilateral motor and sensory block up to the costal margins (1955). A, thigh, completely relaxed. B, right side of chest, moderate hypertonicity.

prominent; and with the higher rate, muscle relaxation became complete. (Fig. 4B.) No fasciculations were observed. The sensitivity to succinylcholine chloride was considered normal.

Spinal anesthesia with Pontocaine®: A bilateral sensory and motor block up to the costal margins was induced. Complete relaxation was attained and the electromyogram showed no activity. (Fig. 5.) As the anesthesia wore off in about five hours the muscular rigidity returned. For about two hours the spasms were intense, causing the patient to be quite disturbed and uncomfortable.

Abstract of personal history and psychiatric findings: The patient was born in a rural area in Tennessee, the youngest of four children. The mother died when he was one year old. The father, a sharecropper, remarried three years later; he had five children by the second wife. At times the patient described his father and stepmother as kind, but his early memories involved mainly instances of rejection and harsh punishment. From nine to eleven years of age, he lived with an aunt in West Virginia, but he then rejoined his father and stepmother who had moved to Ohio. When he was seventeen years old he returned to West Virginia where he worked in the coal mines for several years; later he was a professional gambler until he entered the Army at thirty-four years of age. During the years as a gambler and later in the Army he was constantly in a state of tension and recalled dreadful headaches. The patient married at age twenty-five, but he and his wife separated periodically. On these occasions his wife "usually became angry and returned to her mother," frequently for as long as a year. He was not aware of having been overtly upset by this pattern. He had numerous "girl friends," one of whom gave birth to his only child. He felt most

attached to this girl friend and the young daughter, and often lived with them when his wife was gone. He became very upset when his girl friend and the young daughter left him in 1953 as he was becoming ill. Following his discharge from the hospital the patient was content not to work, expressing the sentiment that he had lived a full life. The intermittent separations with his wife and girl friend continued.

It was concluded that the patient's personality problems included a fear of struggle, strong passive dependency wishes with a fear of the loss of maternal figures and repressed hostility.

COMMENTS

It appears justifiable, at least in the present state of our knowledge, to classify this patient as having the stiff-man syndrome. His outstanding manifestations of fluctuating muscular rigidity and painful spasms were strikingly similar to patients described by Moersch and Woltman [*1*] and others [*2–8*] as having this entity. However, significant discordancies should be emphasized. The neuromuscular disorder in our patient (P. V.) was not "progressive," as described in some of the other cases. Moreover, the severe spasms and incapacitating rigidity in our patient diminished subsequent to treatment of the hyperthyroidism, although moderate hypertonicity persisted apparently at a fixed stage. The biopsy specimen of the muscle was non-contributory. In three reported cases of the stiff-man syndrome the muscles have demonstrated various abnormalities: increase in fibrous or collagen tissue, sarcolemnal hyperplasia and muscle degeneration [*2,4,8*]. However, a normal biopsy specimen has been found in three patients [*1,7*]. Unfortunately, in our case, a repeat muscle biopsy could not be performed to determine if any abnormality might have developed during the several-year period of observation. Our patient showed a normal decrement in serum phosphorus following the administration of insulin, which is in contrast to the patient described by Price and Allott [*7*], but in keeping with the normal fall in serum phosphorus following the administration of glucose in the patient described by Whalen et al. [*8*]. A reducing substance was never present in the urine of our patient, a variable finding in some of the other patients described. Relaxation could be obtained by the administration of succinylcholine chloride and spinal anesthesia, in contrast to the patient described by Whalen et al.

Finally, none of the other reported cases of the stiff-man syndrome were assumed to be associated with hyperthyroidism, however the descriptions of a few of the reported cases are very suggestive of hyperthyroidism. In the case described by Ornsteen [*2*] there was progressive weight loss, drenching sweats and tachycardia up to 160, with spasms. The latter were markedly aggravated by emotional difficulties and the patient himself referred to his symptoms as "stage fright" and "freezing up." Profuse sweating was mentioned in three other cases [*4,6,7*]. The basal metabolic rates were reported as plus 56, plus 65 and plus 77 per cent in three cases described by Moersch and Woltman [*1*], although the authors attributed the elevated rates to muscular activity.

Conversely, it is important to emphasize that extensive muscular rigidity and myoclonic spasms have been described in hyperthyroid patients previously, albeit rarely. Particularly notable was the case described by Bathhurst [*9*] which is also generally considered to be the first published report of chronic thyrotoxic myopathy. Bathhurst stated in the description of his patient " . . . the muscles on the right side in the lumbar region are greatly thickened and feel like contracted tendons. The spine is kept absolutely rigid and cannot be flexed; this as in the case of the neck is due to the contracted condition of the erector spinae. There is considerable lordosis of the lumbar spine . . . Dr. Beevor . . . regarded the contracted condition of the erector spinae as most unusual." The course of Bathhurst's patient was not mentioned. More recently, lesser degrees of muscular stiffness and cramps have also been noted [*10–12*] in an occasional patient with chronic thyrotoxic myopathy. Sattler [*13*] and Riese [*14*] described patients with hyperthyroidism with myoclonic spasms and stiffness of the vertebral column and generalized rigidity respectively. Zondek [*15*] and Wohl and Shuman [*16*] have called attention to patients with chronic thyrotoxic encephalopathy (coma Basedowicum) in whom stupor developed in conjunction with generalized spasticity. In addition, it is well known that typical Parkinsonism with concomitant rigidity may be associated with hyperthyroidism [*17*].

It is difficult to reconcile at this time the various conflicting findings noted as part of the stiff-man syndrome. It may eventually be demonstrated that basically different conditions have been described or that the variables represent different stages or variants of one primary disease. Until more information is at hand, it

would seem advantageous to continue to include in the stiff-man syndrome patients who demonstrate the predominate picture of severe fluctuating rigidity and spasms.

Two main points can be derived from the observations in the case reported here. The first is that an associated hyperthyroidism should be given serious consideration in a patient with fluctuating muscular rigidity and myoclonic spasms, i.e., the stiff-man syndrome, since improvement of the neuromuscular disorder might follow relief of the hyperthyroidism.

The second point concerns a theoretic consideration of the etiology of both conditions, namely, the implication of an associated hypothalamic dysfunction. The studies which were performed on our patient suggested that the abnormal impulses emanated from the central nervous system. The electromyograms revealed only rapid discharges and the response to anesthesia was essentially normal. The severe myoclonic jerks were accompanied by profuse sweating, hypertension and tachycardia, intimating a connection with the autonomic nervous system. Furthermore, it is significant that the hypertonicity in our patient continued after he became euthyroid. This would be consistent with the possibility that the hypothalamic dysfunction causing the muscular disturbance was mediated separately from thyroid activity *per se*, although apparently aggravated by the increased thyroid function. The combination of hyperthyroidism and typical Parkinsonism has provided similar evidence [*17*].

SUMMARY

A case of severe fluctuating muscular rigidity and myoclonic spasms, an example of the stiff-man syndrome in association with hyperthyroidism is described. Treatment of the hyperthyroidism was followed by a decrease in the marked generalized muscular rigidity and spasms, but moderate hypertonicity persisted.

Extensive studies did not reveal the specific nature of the neuromuscular disturbance but were consistent with a central nervous system origin.

Acknowledgment: We are indebted to the resident staff for the years 1953 and 1954 and to Dr. R. Goldsmith for their participation and interest in the care of the patient described; to Dr. E. F. Van Maanen for his assistance in the pharmacologic studies, and to Drs. S. Kaplan and W. D. Ross for their participation and aid in the psychiatric evaluation.

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Leishmaniasis of the Larynx*

Report of a Case and Its Confusion with Histoplasmosis

HORACE H. ZINNEMAN, M.D., WENDELL H. HALL, M.D., PH.D.
and FRANKLIN G. WALLACE, PH.D.

Minneapolis, Minnesota

ANY case of leishmaniasis found within the limits of the continental United States of America appears well worth reporting because of the rarity of the disease in this country. The clinical manifestations in our patient were not suggestive of leishmaniasis and appeared to be of a type hitherto unreported. The histologic appearance of the lesions initially led us to confuse the disease with histoplasmosis, an error which has been committed repeatedly elsewhere. Eventual recognition of leishmaniasis led to successful treatment with tartar emetic (potassium and antimony tartrate).

CASE REPORT

A forty-two year old white machine operator noted the gradual onset of hoarseness in the Spring of 1950. Local therapy with tincture of iodine was of no avail, and by September 1950 he had become increasingly short of breath. A choking spell necessitated tracheotomy. Following the operation his voice began to improve and was almost normal by the Spring of 1951. Very gradually he again became hoarse, and by February 1952 his voice had diminished to a whisper. There also were intermittent episodes of fever. He encountered considerable difficulty in swallowing and lost 25 pounds of weight.

The patient had lived all his life around Duluth, Minnesota. From 1943 to 1944 he saw action as a soldier in North Africa and Italy. He left the United States by air on April 17, 1943, stopped briefly at Trinidad and at Belem, Brazil, and spent six or seven days at Natal, Brazil. He then proceeded to North Africa where, besides stops of one to four days each at Dakar, Marrakesh, Casablanca, Oran and Port Lyautey, he spent a month or more at Rabat, Morocco and Djedeida, Tunisia.

On July 18, 1943, he was shot down in Italy and was made a prisoner of war. He remained in a camp near Ancona until September 15 when he escaped and spent the next fifty-four days traveling on foot to Bari, where he rejoined the Allied Forces. Then, after remaining nearly a month at various points in North Africa, he was repatriated. During his wanderings in Italy he had a slowly-healing cutaneous ulcer on the lower part of his right leg.

Upon admission to the Minneapolis Veterans Administration Hospital in March 1952 the patient was afebrile, alert, but poorly nourished; he weighed 125 pounds. He was unable to speak above a whisper. There was generalized swelling and reddening of the mucosa of the hard palate, maxillary gingiva, tonsillar pillars, tongue, uvula and the posterior pharyngeal wall. (Fig. 1.) The mucosa was granular in appearance and of spongy consistency. There was no ulceration in these areas. Similar lesions were also seen in the larynx; the vocal cords were swollen, granular, and covered with a dirty gray exudate. The heart and lungs were normal in appearance. The blood pressure was 95/70 mm. Hg. The liver, spleen and kidneys were not palpable. Results of the rectal examination were normal. There were no skin lesions.

The initial urinalysis was within normal limits. The hemoglobin was 14.1 gm. per 100 ml., and the leukocyte count was 4,000 per cu. mm. with 58 per cent neutrophils, 34 per cent lymphocytes, 3 per cent monocytes, 3 per cent eosinophils and 2 per cent basophils. The erythrocyte sedimentation rate was 38 mm. per hour. The serum albumin was 2.1 gm. per 100 ml., alpha globulins 1.5 gm. per 100 ml., beta globulins 2.1 gm. per 100 ml. and gamma globulins 2.1 gm. per 100 ml. Results of liver and kidney function tests were within normal limits. Sputum cultures were negative for acid fast organisms and fungi. The spinal fluid revealed no abnormalities. Roentgenologic examinations of the chest and the gastrointestinal tract were within normal limits. A sternal bone marrow biopsy specimen revealed one non-specific granuloma. Two of four biopsy specimens (hematoxylin and eosin stain) of the mucous membrane of the palate and pharynx revealed numerous chronic inflammatory cells with occasional giant cells of the Langhans' type. A few foci of macrophages, with many intracytoplasmic bodies which seemed to be

* From the Veterans Administration Hospital, and the Departments of Medicine and Zoology, University of Minnesota, Minneapolis, Minnesota. Manuscript received August 18, 1960.

FIG. 1. One small and one larger granuloma of the tongue. The pharynx and larynx were involved more extensively.

enclosed by capsules, were seen immediately beneath the epithelium. (Fig. 2.) A presumptive diagnosis of histoplasmosis was made [*1*]. Attempts to isolate the fungus from the biopsy material by cultural and animal inoculation were unsuccessful.

Two courses of therapy with ethyl vanillate coincided with appreciable improvement. The patient was able to return to work. His symptoms and complaints soon recurred, however, and in December 1954 he was hospitalized with an acute tracheal obstruction which necessitated emergency tracheotomy. He was dyspneic and had a laryngeal stridor. The tongue and oropharynx were swollen. He had a temperature of 100°F. The urine was normal, the peripheral leukocyte count was 2,800 per cu. mm. (64 per cent neutrophils), the hemoglobin 16.8 gm. per 100 ml., and the erythrocyte sedimentation rate was 2 mm. per hour. Results of liver and kidney function tests were within normal limits.

By that time serious doubts had arisen concerning the diagnosis of histoplasmosis, which had been made solely on the strength of histologic tissue preparations. Results of cultures, serologic complement fixation tests, and even the histoplasmin skin test, had remained consistently negative. For these reasons an additional biopsy specimen was taken from the larynx for slide imprints and cultures. These preparations (Giemsa's stain) showed kinetoplasts within the organisms. (Fig. 3.) On March 1, 1955, another laryngeal biopsy was performed and N.N.N. culture tubes were inoculated with some of the tissue. On March 10 one tube was weakly positive (Fig. 4) but subcultures died out.

A hamster was inoculated intraperitoneally from

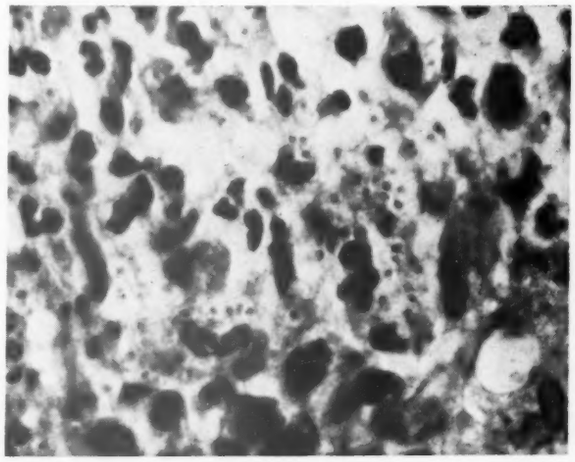

FIG. 2. A biopsy specimen of the vocal cords stained with hematoxylin and eosin contains numerous organisms of leishmania. Original magnification × 793.

the same biopsy specimen and on May 2, sixty-two days later, a portion of its spleen was removed. A heavily infected cell was found in imprint preparations in about every tenth field. The hamster was sacrificed after ninety-seven days. The remaining portion of the spleen was not enlarged and organisms were extremely rare. Subinoculations to two new hamsters were fruitless, and cultures from the original animal died out. The apparent spontaneous cure in the hamster and the feeble growth in culture suggest that the strain of organisms was not highly virulent.

After the diagnosis of leishmaniasis had been established, the patient was treated with two successive courses of 5 mg. of 2-hydroxystilbamidine administered intravenously. The laryngeal swelling decreased greatly but failed to disappear entirely. For this reason it was decided to add a course of 1.2 gm. of sodium and antimony tartrate administered intravenously in divided doses at two-day intervals.

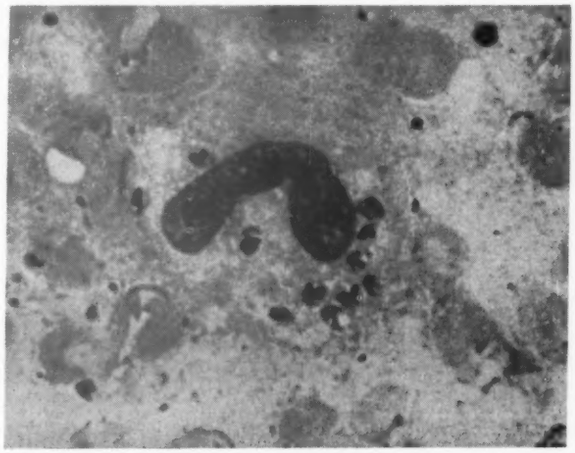

FIG. 3. A slide imprint preparation shows many of the leishmanias with Giemsa stain. Note the clearly defined kinetoplasts. Original magnification × 610.

FIG. 4. A leptomonad form of leishmania cultures on N.N.N. medium from a biopsy specimen. Original magnification × 1,220.

With this therapy, the laryngeal swelling disappeared completely, the patient felt entirely well and the tracheotomy was closed. He took up his previous occupation and had no further complaints. He has gained 35 pounds since his discharge in 1955. His vocal cords are scarred but not otherwise abnormal. His voice has returned but there is a considerable amount of hoarseness. He was last examined in May 1960.

COMMENTS

From the time of the recognition of histoplasmosis by Darling in 1902, it has been subject to confusion with leishmaniasis. Darling's search for leishmaniasis in the Panama Canal Zone led to his original description of histoplasmosis. Although Darling recognized the disease as an entity apart from kala-azar, he believed the organism to be a new protozoan [*2–4*].

In 1925 Watson and Riley investigated the tissues of a woman who had lived in Minnesota throughout her life and died of a febrile disease with leukopenia, hepatomegaly and splenomegaly. The histologic appearance of the lesions suggested the diagnosis of kala-azar [*5*]. Further study convinced Watson and Riley that they were dealing with the organism described by Darling. Thus they were able to report the first case of histoplasmosis found within the continental limits of the United States, and to dispel the then current concept of histoplasmosis as a tropical disease [*6*]. After successful culture by DeMonbreun in 1934 [*7*] Histoplasma capsulatum was recognized as a fungus.

Leishmaniasis, on the other hand, has been repeatedly mistaken for histoplasmosis [*1,8–10*]. In most erroneous reports the diagnosis was based mainly on the histologic appearance of the hematoxylin and eosin-stained tissue. The earlier use of auxiliary tests would have clarified the diagnosis. Tissue sections may be used for the differentiation between histoplasmosis and leishmaniasis when the periodic acid-Schiff stain is used. The carbohydrates of the capsule of H. capsulatum will accept the stain and appear distinctively pink. This finding will be absent in leishmaniasis. Giemsa's stain differentiates the agent from H. capsulatum by revealing the characteristic kinetoplast of leishmania in sections and, more clearly, in imprint or smear preparations.

In the case of active histoplasmosis, the patient's serum will fix complement in the presence of the yeast antigen or histoplasmin. Delayed skin sensitivity to histoplasmin is present in practically all cases of histoplasmosis with the exception of the acute, disseminated form. It is negative in leishmaniasis. The final and decisive differentiation is made by means of culture. Whereas H. capsulatum grows on blood agar media, leishmania requires the standard N.N.N. medium or other similar media, such as the one described by Conrad, Manson and Peterkin [*11*], or chick embryo cultures [*12*]. The leptomonad forms grow at 22 to 24°C. within two to three weeks. The three species of leishmania cannot be differentiated morphologically, either in tissue or in culture. The reaction in experimental animals is of slight value and subject to great variation between strains of the same species. The clinical picture and geographic origin are the most dependable criteria [*13*].

Mucocutaneous leishmaniasis caused by Leishmania braziliensis almost always begins as a cutaneous ulcer and sometimes causes ulceration of the mucous membranes of the mouth, nasopharynx and pharynx with destruction of underlying tissue and cartilage. This involvement may occur by direct extension or by metastasis. The infection occurs in South and Central America. Barbosa (quoted by Pessoa [*14*]) classified 1,791 cases of mucosal involvement in Brazil and noted only one case in which the lesions of the larynx were similar to

the case reported herein.* According to Fuller and Geiman [*15*], L. braziliensis is non-infectious to the hamster.

Oriental sore, or cutaneous leishmaniasis caused by L. tropica, typically appears as a single ulcer on the skin of an exposed part of the body. A few cases of involvement of the mucous membranes are reported. LaCava [*16*] and Cardamatis and Melissides [*17*] described cases in which the ulceration extended from the skin onto the lips or nose. Brumpt [*18*] described a case of stenosis of the esophagus associated with two oriental sores, one on the finger and one on the foot. While the leishmanial nature of the esophageal lesion was not proved, it was cured by treatment with urea-stibamine as were the two sores. Trifilo [*19*] cites a case of L. tropica ulcer on the tongue. Oriental sore occurs in Central and Southwestern Asia, and the countries bordering the Mediterranean. Distribution is localized within these general areas and almost nowhere overlaps in detail the distribution of visceral leishmaniasis. Both diseases may occur in a given country [*20*].

Kala-azar, or visceral leishmaniasis caused by L. donovani, involves the reticuloendothelial cells of the liver, spleen, bone marrow and, less commonly, the intestine, skin, or almost any organ of the body. Angevine et al. [*21*] and Bell et al. [*22*] cite cases of asymptomatic infection of the lymph nodes alone. Forkner and Zia [*23*] report the occurrence of L. donovani in the nasal mucosa and the tonsil. Meira Lins [*24*] reports infantile cases in which there is invasion of the respiratory tract. Dastidar [*25*] reports a tongue lesion caused by this parasite.

Our patient exhibited an unusual clinical picture that is approximated by rare cases of each of the three types of leishmaniasis, and he had at least brief exposure in an edemic area of each within a period of eight months. His exposure in South America was negligible. He spent a few hours at Belem and a week at Natal in the relatively sheltered surroundings of military air fields. These cities are not in important endemic areas of mucocutaneous leishmaniasis [*14,26*]. The patient's travels in North Africa and Italy were within the general endemic zone of oriental sore. However, his principal base in Africa (Djedeida) is in northern Tunisia, whereas oriental sore occurs only in southern Tunisia [*20,27,28*]. His other stations in North Africa, with the possible exception of Algiers where he spent only two days, were not in important endemic centers of either form of leishmaniasis. Judging from the personal observations of one of us (F. G. W.) and the number of reports in the literature, cases of cutaneous leishmaniasis were not commonly seen in American soldiers who served in North Africa and Italy. One such case was reported by Auerbach and Buchholz [*29*]. Most of the cases of cutaneous leishmaniasis in American service personnel originated in the Persian Gulf area [*30,31*]. In view of the nature of some of the cases cited, the presence of an ulcer on the leg of an undetermined nature in our patient and his wanderings in endemic areas in Italy make it impossible to rule out L. tropica as the cause of his illness.

Visceral leishmaniasis also occurs in the Mediterranean region and is endemic in northern Tunisia where the patient was based for the longest time. At least twenty-three cases were reported in American soldiers from the Mediterranean theater [*32*]. It also is distributed to some extent in the part of Italy where our patient walked for such an extended period. The literature shows that L. donovani may invade many different organs and may cause widely different syndromes. The hamster experiment, while inconclusive, is compatible with the identification of the organism as a strain of L. donovani of low virulence. Our conclusion is that this was probably an abortive infection with L. donovani.

SUMMARY

A case of leishmaniasis was initially misdiagnosed as histoplasmosis on the basis of the histologic similarity. This error could have been avoided if a special carbohydrate stain had been used for the histologic preparations, if imprints of the biopsy material had been examined with a Giemsa stain, and if the importance of negative histoplasmosis skin sensitivity, serology and cultures had been heeded in the initial stages of the clinical investigation of this patient.

The case was unusual in that only the larynx was affected. While the possibility that L. tropica was the pathogen cannot be ruled out, it is suggested that L. donovani was probably the species concerned.

Treatment with potassium and antimony tartrate caused the pharyngeal and laryngeal granulomas to heal.

* After submission of this paper, an additional case of leishmaniasis of the larynx, but with a nasal ulcer, was reported by Jaffe [*33*].

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Hyperinsulinemia in L-Leucine-Sensitive Hypoglycemia in an Adult*

SHIRLEY WEISENFELD, M.D. *and* MARTIN G. GOLDNER, M.D.
New York, New York

COCHRANE, Payne, Simpkiss and Woolf [*1*] in 1956 were the first to describe a type of hypoglycemia in children which was precipitated or aggravated by feedings containing L-leucine. They suggested two possible mechanisms for this action of L-leucine: (1) enhancement of the effect of circulating insulin on carbohydrate metabolism, (*2*) increased secretion of insulin by the islets of Langerhans. Cochrane has since extended his observations and postulations regarding possible mechanisms [*2–4*]. Others have confirmed the existence of L-leucine-induced hypoglycemia [*5–9*] and data have been presented which help to elucidate the pathway(s) of its production [*1–4,8–10*].

In this study we shall present observations which support the concept that L-leucine induces hypoglycemia by stimulating the secretion of insulin by the pancreas. Of further interest is the circumstance that our observations were made in an adult who suffered from severe hypoglycemia of recent onset and whose symptoms were highly suggestive of an islet cell adenoma.

CASE REPORT

N. C., a forty-two year old white man, was first admitted to the hospital on July 6, 1959, because of recurring attacks of generalized weakness, cold sweats, nausea, dizziness, staggering gait, perioral numbness, diplopia and slurred speech. The attacks had started six to eight months prior to admission, gradually increasing in severity and frequency. They always occurred when he was hungry, especially in the evenings, and were relieved very rapidly by the ingestion of food or candy. He had gained 16 pounds in six months due to increased hunger and appetite associated with these attacks and to frequent carbohydrate feedings as recommended by his family physician. He never had experienced convulsions or unconsciousness. Because of several low fasting blood sugar concentrations, his personal physician had referred him to one of us (M. G. G.) for evaluation.

The patient had had a normal childhood and his past history was non-contributory. His parents, five brothers and an only son were well and had never experienced convulsions or any attacks such as his. There was no family history of diabetes.

Physical examination revealed an alert middle-aged white man, well developed and well nourished. The pulse was 72 per minute and regular, the blood pressure was 120/80 mm. Hg. There were no abnormal physical findings. There was no abnormal pigmentation of skin or mucous membranes.

Laboratory data were all within the normal limits except for consistently low fasting blood sugar levels (34 to 65 mg. per 100 ml.). Roentgenogram of the chest, gastrointestinal x-ray series, and the electrocardiogram were within normal limits. The results of special tests relating to carbohydrate metabolism (glucose tolerance, glucagon response and L-leucine response tests, and plasma insulin levels) will be presented in detail later.

A diagnosis of probable islet cell adenoma was made. The patient refused surgery, leaving the hospital after four days, but promised to return at a later date for exploration of the pancreas.

He was then followed up on an outpatient basis. Attacks continued as before and were easily precipitated by prolonged fasting. He gained another 15 pounds in nine months. Fasting blood sugar levels ranged between 25 and 60 mg. per 100 ml. Whenever tested with oral L-leucine, symptoms of hypoglycemia developed, identical with those accompanying his attacks; on one occasion there were mild convulsions followed by amnesia for the episode. All symptoms and signs were rapidly relieved by the oral or intravenous administration of glucose. Moderate restriction of leucine-containing nutrients, particularly cheese, failed to alter the patient's course.

In April 1960, the patient was readmitted to the hospital for pancreatic surgery. Except for moderate obesity (he was 35 pounds above his usual weight), the physical findings were all within normal limits.

* From the Departments of Medicine of the Jewish Chronic Disease Hospital, and the State University of New York, Downstate Medical Center, Brooklyn, New York. This investigation was supported in part by a grant from Charles Pfizer & Co. Manuscript received August 4, 1960.

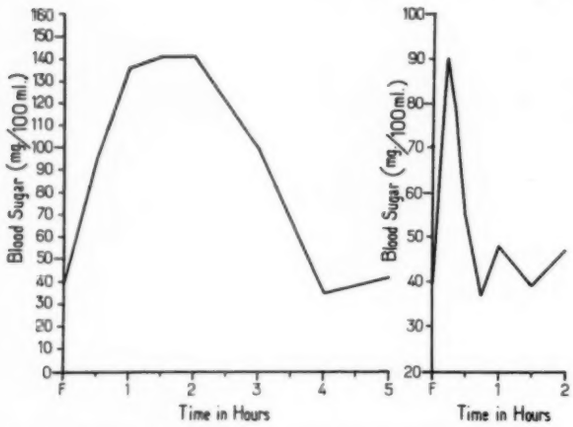

FIG. 1. Patient N. C. Blood sugar response to the administration of 100 gm. glucose orally (left) and to 0.1 mg. glucagon intravenously (right). Tests were made about nine months prior to surgery.

Fasting blood sugar levels were 30, 41 and 48 mg. per 100 ml. There was one episode of sweating, mental confusion, twitching and vomiting after a fourteen-hour fast. This was relieved by the oral administration of glucose.

On April 18, 1960, pancreatic exploration was performed.* The tail of the pancreas was somewhat irregular but no definite tumor could be identified in any part of the pancreas. Splenectomy and subtotal pancreatectomy were performed. Despite many sections, no gross or microscopic tumor could be delineated. The pancreatic tissue appeared normal on both gross and microscopic examination. The islets of Langerhans were described as "abundant, but not hyperplastic, with well granulated B cells and numerous A cells."

The postoperative course was complicated by spiking fever due to infection in the operative area and thrombophlebitis following a venous cut-down. These complications cleared with antibiotic therapy. There have been no postoperative severe hypoglycemic symptoms, except for one occasion when Parenamine® was given intravenously in 5 per cent glucose, but there were frequent cold sweats upon arising in the morning. The patient was discharged from the hospital on May 31, 1960.

METHODS AND MATERIAL

During his first admission the patient was given a five-hour oral glucose tolerance test, using 100 gm. glucose, and an intravenous glucagon response test, using 0.1 mg. crystalline glucagon.† Capillary blood samples were analyzed for sugar concentration by the method of Somogyi and Nelson [*11*]. The blood sugar and plasma insulin response to L-leucine was also studied. This patient and four adult hospitalized patients used as controls (two diabetic and two non-diabetic) were given 0.15 gm. L-leucine per kg. of body weight orally. L-Leucine* was given mixed in a small amount of water, with lemon juice and saccharine added. Capillary blood samples were analyzed for sugar concentration except when the studies included analysis for plasma insulin concentrations. In these instances heparinized venous blood was drawn and a sample taken for immediate blood sugar determination. The plasma was then removed after centrifugation and frozen until the insulin concentration could be measured.† Insulin concentrations of our patient's fasting blood were determined in a like manner.

RESULTS

Glucose Tolerance. As seen in Figure 1, the oral glucose tolerance test demonstrated adequate absorption of the glucose via the gastrointestinal tract. However, the curve is abnormal since it starts at a hypoglycemic level and the peak is at one and a half and two hours, with a return to the hypoglycemic fasting level by four to five hours.

Glucagon Response. The response of the blood sugar concentration to intravenously administered glucagon is shown in Figure 1. There is a rapid increment of 52 mg. per 100 ml. and then a quick return to the previous hypoglycemic level. This is a normal hyperglycemic response as determined in our laboratory [*13–15*] and suggests the presence of hepatic glycogen and no impairment of glycogenolytic pathways. However, the abnormally rapid return to the previous hypoglycemic level is similar to the curves of patients with islet cell tumors described by Marks [*16*]. We generally see a return to normal by 90 to 120 minutes [*13–15*].

Response to L-Leucine. Figure 2 demonstrates changes in the blood sugar and plasma insulin concentrations following administration of L-leucine to our patient and to four other adult hospitalized patients. Whenever measured, our patient's blood sugar concentration fell and his plasma insulin level rose following the administration of L-leucine. The second test in our patient had to be discontinued because of convulsions.

One of the four control patients (J. K.), a mild diabetic, showed a moderate and delayed

* Dr. M. Ratzan, who referred this patient to us, performed the surgery.

† Crystalline glucagon was kindly supplied by Dr. W. R. Kirtley of the Lilly Research Laboratories.

* L-Leucine was kindly supplied by Dr. D. G. Iezzoni of Charles Pfizer & Co.

† All plasma insulin concentrations were deter nined by Dr. R. Yalow and Dr. S. Berson, by their immunoassay method [*12*].

TABLE I
PRE-SURGICAL FASTING BLOOD SUGAR AND PLASMA INSULIN CONCENTRATIONS IN PATIENT N. C.

Date	Blood Sugar (mg. per 100 ml.)	Plasma Insulin (microunits per ml.)
7-10-59	65	28
7-23-59	25	38
2-9-60	61, 63, 61	145, 103, 100
3-16-60	27	76
3-17-60	33	120

TABLE II
POST-PARTIAL PANCREATECTOMY BLOOD SUGAR CONCENTRATIONS

Date	Blood Sugar (mg. per 100 ml.)	Remarks
4-19-60	101	Receiving 5% glucose i.v.
4-20-60	206	Receiving 5% glucose i.v.
4-22-60	157	Receiving 5% glucose i.v.
4-25-60	73	Receiving 5% glucose i.v.
4-27-60	28	Receiving 5% glucose, i.v. with Parenamine®—mild symptoms of hypoglycemia present
4-29-60	118	Receiving 5% glucose i.v.
5-2-60	103	Receiving 5% glucose i.v.
5-5-60	83	9 A.M. non-fasting specimen
	77	12 noon non-fasting specimen
	98	3:45 P.M. non-fasting specimen
5-6-60	137	9:30 A.M. non-fasting specimen
	90	12:15 P.M. non-fasting specimen
5-9-60	85	9:00 A.M. non-fasting specimen
5-11-60	35	8:45 A.M. 11 hour fast—no symptoms of hypoglycemia
5-18-60	25	Overnight fast—no symptoms of hypoglycemia
5-25-60	59	8:30 A.M. non-fasting specimen
	69	10:30 A.M. non-fasting specimen
	85	3:30 P.M. non-fasting specimen
5-26-60	85	8:15 A.M. non-fasting specimen
6-23-60	46	11:00 A.M. 12 hour fast—no symptoms of hypoglycemia
7-21-60	40	10:00 A.M. overnight fast—no symptoms of hypoglycemia

fall of blood sugar after the administration of leucine. The others showed no alteration. Plasma insulin concentrations were determined in one of these leucine-insensitive patients (E. B.) and no significant change was noted.

Fasting Plasma Insulin Concentration. As seen in Table I, our patient's preoperative fasting plasma insulin concentrations were normal or

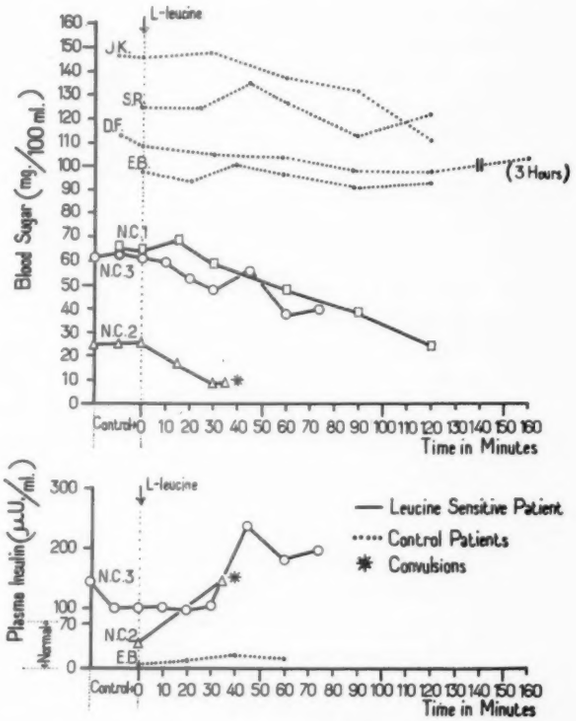

FIG. 2. *Top*, blood sugar and *bottom*, the plasma insulin response to oral administration of 0.15 gm. L-leucine/kg. body weight. Straight lines represent results on the patient reported, N. C.; interrupted lines represent results on two mild diabetic patients (J. K. and S. R.) and two non-diabetic patients (D. F. and E. B.); N. C. 1, N. C. 2 and N. C. 3, indicate three tests on the same patient. All tests were made several months prior to surgery. In tests E. B., N. C. 2 and N. C. 3, both blood sugar and plasma insulin levels were determined on the same samples of blood, so that their changes can be correlated by comparing the simultaneous curves in the upper and lower graphs.

high on different occasions. The corresponding fasting blood sugar levels are included. The normal fasting plasma insulin level has been found to range from 0 to 70 microunits per ml. by Yalow and Berson [*10*]. The normal range for fasting blood sugar concentration in this laboratory is 70 to 110 mg. per 100 ml. The plasma insulin level was not always high when the fasting blood sugar was very low.

Postoperative Blood Sugar Levels. In Table II are included blood sugar levels determined during the first three months after surgery. The sugar concentrations were normal or slightly elevated while the patient received glucose infusions intravenously or was in a non-fasting state. Fasting levels were as low as they had been preoperatively. On one occasion, while receiving 100 ml. of Parenamine together with 5 per cent

glucose in water intravenously in an attempt to improve his nitrogen balance, mental confusion, sweating and personality changes developed. The blood sugar level was determined and proved to be very low (28 mg. per 100 ml.). Parenamine is an acid hydrolysate of casein and contains 15 gm. of amino acids in 100 ml. According to the manufacturer's analysis, it has 11.6 per cent leucine, 6.1 per cent isoleucine, 7.3 per cent valine, and 8.2 per cent lysine in addition to smaller quantities of another essential and non-essential amino acids.

COMMENTS

Cochrane [*4*] has recently reviewed the clinical entity of L-leucine-sensitive hypoglycemia of children. We should like here to review the literature pertaining to its symptomatic or asymptomatic occurrence in adults, its possible relation to islet cell adenoma, and evidence for and against insulin secretion as one of the underlying mechanisms.

L-Leucine Sensitivity in Adults. On searching the literature we found reports of five instances of L-leucine-induced hypoglycemia in parents of L-leucine-sensitive children [*1,2,4,9*]. Although asymptomatic as adults, three gave a history of childhood convulsions. Cochrane has already stressed the familial nature of this disorder. The only other adults with L-leucine-induced hypoglycemia have been two patients described by Schwartz and co-workers [*6*]. Both patients had symptomatic hypoglycemia of recent onset, fasting hypoglycemia and proved islet cell tumors, one benign and one malignant.

Ours is the eighth case of adult L-leucine-induced hypoglycemia. Although an islet cell tumor was not found during surgery, we believe, for reasons to be discussed later, that our patient does have a small adenoma still present in the head of the pancreas and that he falls into the same category as the patients of Schwartz.

L-Leucine Sensitivity and "Functional" Versus "Organic" Hypoglycemia. Since most cases of infantile or juvenile hypoglycemia are considered idiopathic or "functional" in nature, i.e., no histologic abnormalities are demonstrable in the pancreas, few patients are subjected to surgical exploration. Therefore, in approximately two dozen juvenile cases of leucine-induced hypoglycemia mentioned in the literature, the pancreas was examined in only three [*1,4*]. In two, the pancreas was histologically normal, but in the third there was hyperplasia of the islets. Thus, as Cochrane points out, L-leucine sensitivity cannot differentiate between "functional" and "organic" hypoglycemia in children. This must be true in adults as well, as demonstrated by the two categories of adult leucine-induced hypoglycemia already mentioned.

Cochrane estimates that 60 per cent of the patients with infantile or juvenile hypoglycemia are leucine-sensitive [*4*]. Although very few patients with islet cell hyperplasia or tumor have been tested with leucine, there is some evidence that they also vary in their response to L-leucine. In contrast to the two patients of Schwartz mentioned before, Grumbach and Kaplan observed no response to the administration of leucine by one patient with islet cell carcinoma [*9*]; however, the authors do not state whether this was a functioning carcinoma.

Plasma Insulin Levels in L-Leucine-Induced Hypoglycemia. Fasting: In three of the four patients originally described by Cochrane, fasting plasma insulin concentrations were measured by the rat diaphragm method. They were normal in two, but five to six times normal in the third. This was the child previously mentioned whose pancreas showed islet cell hyperplasia [*1*]. Cochrane [*4*] also mentions a patient of Rosenthal with leucine sensitivity who had a normal fasting plasma insulin concentration as measured by the rat diaphragm method.

Yalow and Berson have developed a very sensitive immuno-assay for plasma insulin [*10,12*]. They have reported that five of seven patients with functioning islet cell tumors had fasting insulin levels exceeding 118 microunits per ml. (normal values are up to 70 microunits per ml.) [*10*]. Of six leucine-sensitive patients with hypoglycemia whose plasma they measured for insulin, our patient was the only adult and the only one with elevated fasting insulin concentrations [*17*].

Thus it would seem that fasting hyperinsulinemia is characteristic of "organic hypoglycemia," i.e., islet cell tumor or hyperplasia, and not characteristic of "functional hypoglycemia" associated with L-leucine sensitivity.

Changes in plasma insulin concentration following L-leucine ingestion: Few measurements of plasma insulin have been made in cases of L-leucine-induced hypoglycemia. Using the rat diaphragm method, Behal [*8*] reported a rise of insulin-like activity in one patient's serum within thirty minutes after the ingestion of the standard dose of L-leucine (150 mg. per kg. of body weight).

Quite contradictory to this, Rosenthal, as quoted in a paper by Cochrane [*4*], found no such rise in an L-leucine-sensitive infant, using a similar bio-assay method. However, only one sample of plasma, taken sixty minutes after the administration of L-leucine was tested. A rise may have been missed.

Yalow and Berson, using their more specific immunoassay method, reported abrupt increases in plasma insulin following the ingestion of L-leucine in seven of ten studies in six leucine-sensitive patients with hypoglycemia [*10,17*]. Included were the two patients described by Grumbach and Kaplan [*9*] and the patient described herein. One of the six patients failed to show a significant increase of plasma insulin during each of two leucine tests. Another patient failed to show a rise during the first leucine test but did show an increase of plasma insulin during a second leucine response test. The others showed increases up to 238 microunits per ml., the peak rise occurring ten to forty-five minutes after the ingestion of L-leucine. Control infants and adults failed to show any change in plasma insulin concentration following the ingestion of L-leucine [*17*]. These rises are too rapid to be due to decreased insulin utilization and must indicate that L-leucine increases pancreatic insulin secretion. We are convinced that in some or most patients with leucine-induced hypoglycemia, increased insulin secretion following L-leucine feeding is at least one of the underlying mechanisms.

SUMMARY

A case is reported of symptomatic hypoglycemia occurring in a middle-aged man. In addition to fasting hypoglycemia and fasting hyperinsulinemia, there was a marked hypoglycemic response to orally administered L-leucine. This was accompanied by a rapid rise in plasma insulin.

After partial pancreatectomy fasting hypoglycemia and L-leucine sensitivity persist, even though the patient is essentially asymptomatic at present. No adenoma was identified in the pancreatic tissue removed, but a small tumor may still be present in the pancreatic head.

A review of the literature and information available reveals that juvenile or adult L-leucine sensitivity may occur with the familial "functional" type of hypoglycemia or with "organic" hypoglycemia; that not all patients with juvenile "functional" hypoglycemia are L-leucine-sensitive; that too few patients with functioning islet cell tumor or hyperplasia have been tested to know what proportion of them may be L-leucine sensitive; that fasting hyperinsulinemia is characteristic of islet cell tumor or hyperplasia and not of "functional" L-leucine sensitive hypoglycemia; that at least one important mechanism of L-leucine-induced hypoglycemia is increased pancreatic secretion of insulin.

Acknowledgment: We are deeply indebted to Drs. Rosalyn S. Yalow and Solomon A. Berson for their kind cooperation in performing all plasma insulin assays and for their helpful advice. We are further indebted to Dr. Martyn C. Ratzan for allowing us to study his patient and report our findings, and to Dr. Sydney S. Lazarus of the Department of Pathology of the Jewish Chronic Disease Hospital for his careful study of the pancreatic tissue. We thank Miss Hilda Lawrence and Mrs. Nancy Ruiz for their invaluable technical assistance.

ADDENDUM

Several months after this paper was submitted for publication, this patient (N. C.) returned to work. Shortly thereafter, typical attacks of hypoglycemia recurred, with all the symptoms as before. Fasting blood sugar concentrations were low and two fasting plasma insulin levels were high. The patient was therefore rehospitalized. We are grateful to Dr. Harry Le Veen, Director of Surgery of the Brooklyn Veterans Administration Hospital, who performed an exploratory operation on the patient on April 27, 1961, for the following information. A pancreatic tumor, measuring 1.2 cm. in diameter was removed from the head of the pancreas. Histologic examination by Dr. Gerald Kaufman revealed it to be an islet cell adenoma. Mild diabetes was present for about one week postoperatively. This disappeared, the last fasting blood sugar value being 105 mg. per 100 ml. There has been no hypoglycemia since the adenoma was removed. These findings confirm our belief that this patient had a L-leucine sensitive islet cell tumor rather than functional L-leucine sensitive hypoglycemia because of the presence of fasting hyperinsulinemia.

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Xanthomatous Biliary Cirrhosis Following Chlorpromazine*

NORMAN N. KOHN, M.D. *and* RALPH M. MYERSON, M.D.

Philadelphia, Pennsylvania

IN the vast majority of subjects chlorpromazine hepatitis is benign and of relatively short duration. In the patient to be described, however, jaundice has been extremely prolonged; there has been a marked disturbance of lipid metabolism; and a syndrome indistinguishable from xanthomatous biliary cirrhosis has resulted.

CASE REPORT

A forty-one year old white man (L. J.) was well until early 1958 when, following the death of his parents, vague generalized symptoms developed and he was admitted to another hospital. The physical examination and laboratory studies (including serum cholesterol determination) were within normal limits. The diagnosis of a depressive reaction with anxiety was made and the patient received psychotherapy. Because of an increase in his symptoms the patient was hospitalized on the psychiatric service of the Veterans Administration Hospital, Philadelphia, on October 5, 1959. On admission, the physical examination and routine laboratory studies were within normal limits. The urine contained no bile. An electrocardiogram and roentgenogram of the chest revealed no abnormalities. There had been no recent injections or known exposure to hepatotoxins.

Chlorpromazine therapy, 25 mg. given orally four times daily, was instituted. On the tenth hospital day, because of increasing anxiety, the dosage was increased to 50 mg. four times daily. On the seventeenth hospital day icterus, dark urine and light colored stools were noticed. The patient's symptoms were unchanged from those on admission. Physical examination at this time revealed the presence of an enlarged liver felt 2 inches below the right costal margin.

Shortly after the onset of jaundice the leukocyte count was 11,700 per cu. mm. with 9 per cent eosinophils. The hemoglobin was 15.1 gm. per 100 ml., hematocrit 48 per cent. The urine was positive for bile and negative for urobilinogen. The serum total bilirubin was 12 mg., with 7.6 mg. per 100 ml. direct reacting pigment; serum total cholesterol was 390 mg. per 100 ml. The result of the thymol turbidity test was 0.8 units, the cephalin flocculation test negative. The serum alkaline phosphatase was 37.8 units (Shinowara-Jones), serum transaminase 380 units; serum albumin 3.9 gm. per 100 ml. and globulin 4.1 gm. per 100 ml. The prothrombin time was 100 per cent.

After a period of three weeks of icterus the serum bilirubin level had risen to 41 mg. per 100 ml., with 20 mg. direct reacting pigment. The serum alkaline phosphatase was 68 units and the serum total cholesterol 1,164 mg. per 100 ml. Serum protein electrophoresis was normal. The result of a heterophil antibody test was negative.

Jaundice and laboratory evidence of hepatic dysfunction of an obstructive type persisted throughout the subsequent period of ten months of observation. The significant laboratory abnormalities during this time are summarized in Table I.

Treatment initially consisted of bedrest and administration of a high caloric, high protein diet, low in fat content. A seven-day course of prednisone in 40 mg. daily dosage was begun on the twenty-eighth day of jaundice, without noticeable effect. The patient became progressively more depressed, anorexic and suffered a weight loss of 25 pounds during the first six weeks of hospitalization.

Although the clinical picture was entirely compatible with chlorpromazine jaundice, a potentially correctable surgical lesion could not be ruled out for certain. Accordingly, six weeks after the onset of jaundice, an exploratory laparotomy was performed. At surgery, the entire biliary system was normal to inspection and palpation. The liver was slightly enlarged. Exploration of the common duct revealed no abnormalities. A T-tube was inserted into the common duct and an operative cholangiogram was performed; a wedge of hepatic tissue was taken for biopsy purposes. The cholangiogram was reported to be within normal limits. Grossly, the liver biopsy specimen was mottled green in appearance. Microscopically, there was bile plugging and accumulation of bile in the parenchymal and Kupffer cells. (Fig. 1.) Increased numbers of lymphocytes, granulocytes and plasma cells were present in the portal areas; occa-

* From the Medical Service of the Philadelphia Veterans Administration Hospital, Philadelphia, Pennsylvania. Manuscript received September 7, 1960.

TABLE I
SUMMARY OF LIVER FUNCTION STUDIES

Duration of Jaundice	Serum Alkaline Phosphatase (Shinowara units)	SGOT (units)	Cephalin Flocculation		Serum Total Cholesterol (mg. %)	Serum Bilirubin		Others
			24 Hr.	48 Hr.		Total (mg. %)	Direct (mg. %)	
5 days.....	37.8	390	2+	2+	390	12.0	7.6	...
10 days.....	60.0	...	...	...	...	38.8	19.4	...
30 days.....	82.5	110	...	...	1,164	40.0	15.0	...
2 mo.....	36.1	...	Negative	Negative	...	19.0	8.8	...
3 mo.....	96.0	270	Negative	1+	1,022	15.4	7.2	...
4 mo.....	90.0	440	3+	4+	1,048	18.0	9.2	...
5 mo.....	68.3	130	1+	1+	1,236	14.0	6.0	...
6 mo.....	38.8	90	Negative	Negative	1,560	5.4	2.6	...
8 mo.....	60.5	180	Negative	Negative	1,728	9.6	5.0	SGPT, 102.8 units; serum leucine aminopeptidase, 818 units; one stage prothrombin time; greater than 100%; true prothrombin assay, 400%; proconvertin assay, 400%; proaccelerin assay, 300%
9 mo.....	65.1	570	Negative	Negative	1,800	5.9	3.1	...

sional eosinophils were noted. The biopsy was considered to be compatible with chlorpromazine hepatitis.

Following surgery, and with continuing T-tube drainage of the common duct, an abrupt fall in serum alkaline phosphatase and serum bilirubin levels was noted. (Fig. 2.) Over a period of four weeks, however, the serum alkaline phosphatase returned to its preoperative level. The serum bilirubin, however, never returned to the high preoperative level during the subsequent period of observation. Additional cholangiograms were performed one and two months postoperatively and were within normal limits. Further studies were precluded when the patient inadvertently pulled the T-tube out shortly after the second postoperative study.

Postoperatively, the patient's course was characterized by continuing anorexia, profound depression and weight loss. Despite his poor medical condition, it was decided to attempt a course of electroshock therapy. Nine such treatments were administered in early March 1960. The response was immediate and dramatic. The patient became aware of his surroundings for the first time and was amenable to psychotherapy. His appetite improved, and he regained 20 pounds during a six-week period after the shock therapy. Despite continuing icterus the patient was asymptomatic at this time. However in April 1960 the liver had increased in size to 3 inches below the right costal margin and for the first time the spleen was palpable, extending 1 inch below the left costal margin.

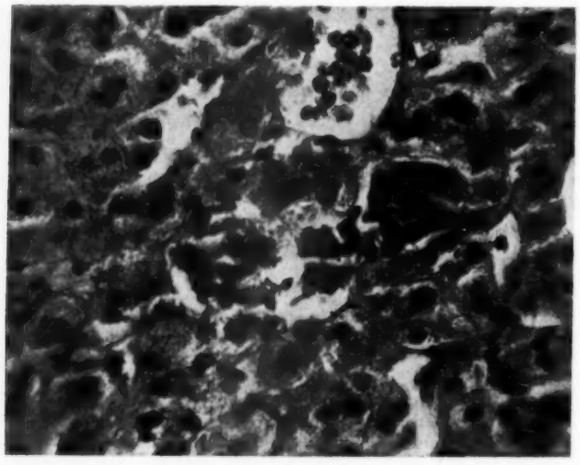

FIG. 1. Biopsy specimen of the liver after six weeks of jaundice showing bile plugging and infiltration with lymphocytes, granulocytes and plasma cells in the portal areas. Hematoxylin and eosin stain, original magnification × 350.

A second liver biopsy was performed on March 22, 1960, on the 150th day of jaundice. (Fig. 3.) Microscopic study of this tissue showed some patchy areas of prominent bile staining within liver cells, canaliculi and Kupffer cells. An occasional bile lake was noted. In a few areas, liver cell karyorrhexis, nuclear enlargement and binucleation were noted. The periportal spaces were slightly enlarged with edema and granulocytic infiltration. The findings were inter-

TABLE II
SERUM LIPID ABNORMALITIES OBSERVED AFTER EIGHT MONTHS OF JAUNDICE

Lipid Fraction	Observed Value	Upper Limit of Normal
Total lipids (mg. %).....	6,800	950
Total cholesterol (mg. %)....	1,765	275
Cholesterol esters (%).....	17	50–75
Phospholipids (mg. %).....	3,450	275
Neutral fat (mg. %).....	1,390	350
Total fatty acids (mg. %)....	3,820	625

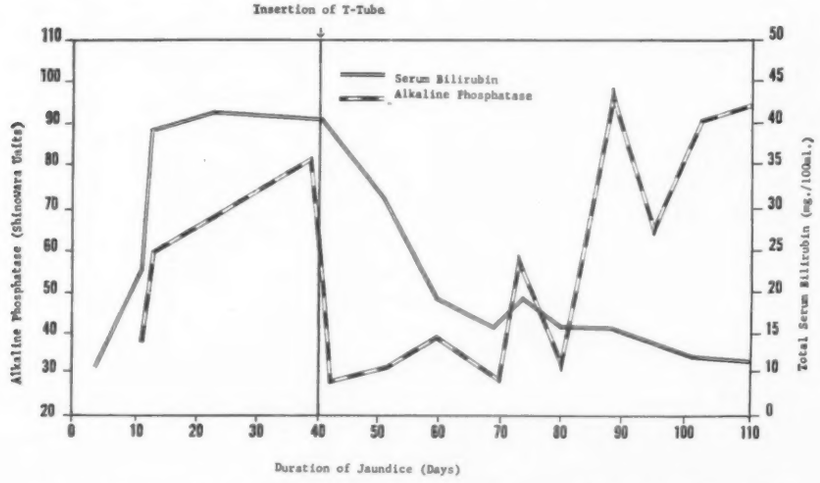

FIG. 2. Changes in bilirubin and alkaline phosphatase levels after insertion of T-tube into common bile duct.

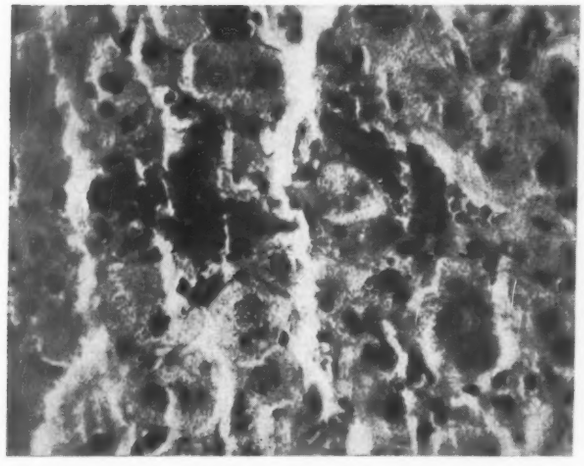

FIG. 3. Biopsy specimen of the liver after 150 days of jaundice showing prominent bile staining within liver cells, canaliculi and Kupffer cells. Occasional bile lakes are present. Hematoxylin and eosin stain, original magnification × 350.

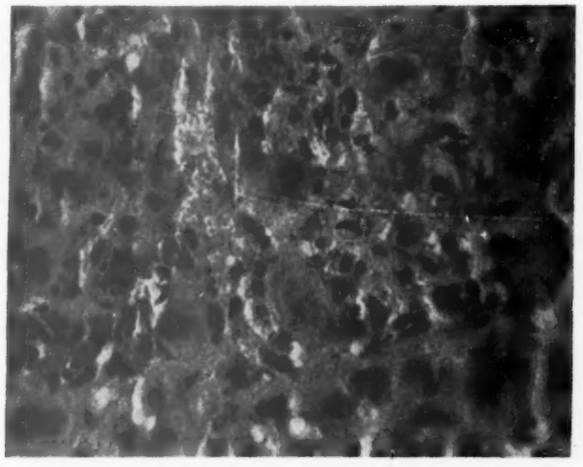

FIG. 4. Biopsy specimen of the liver after 240 days of jaundice showing prominent bile staining with occasional bile granulomas. Scattered focal necrosis is present. Hematoxylin and eosin stain, original magnification × 350.

preted as compatible with prolonged bile stasis due to chlorpromazine therapy.

A second course of prednisone therapy was administered during the sixth month of jaundice. The patient received 60 mg. daily over a thirty day period. During this time there was a slight fall in serum alkaline phosphatase and bilirubin levels, but the serum total cholesterol level remained high. Hepatosplenomegaly persisted and the stools were acholic in appearance.

A third biopsy was performed after 240 days of jaundice. (Fig. 4.) Again, intrahepatic bile stasis was noted. There was patchy necrosis of liver cells. Phagocytosis of bile and small bile granulomas were noted for the first time. A small amount of portal fibrotic reaction was present. At this time a yellow papular eruption appeared suddenly, involving the chest and back principally, with fewer lesions on the nose, eyelids and extremities. (Fig. 5.) Biopsy specimen of one of these lesions showed typical xanthoma. (Fig. 6.)

The results of the patient's serum lipid pattern performed eight months after the onset of jaundice are shown in Table II.* Lactescence of the serum was not present. The addition of ether to the serum, however, produced a dense white flocculum. The results of radioactive fat study employing oral triolein were within normal limits.

As of this writing, the size of the liver has not clinically decreased and the spleen remains enlarged. There has been no roentgenographic evidence of esophageal varices and the electrocardiogram remains within normal limits.

* Kindly performed by Dr. Harry Shay, Fels Research Institute, Temple University School of Medicine, Philadelphia, Pennsylvania.

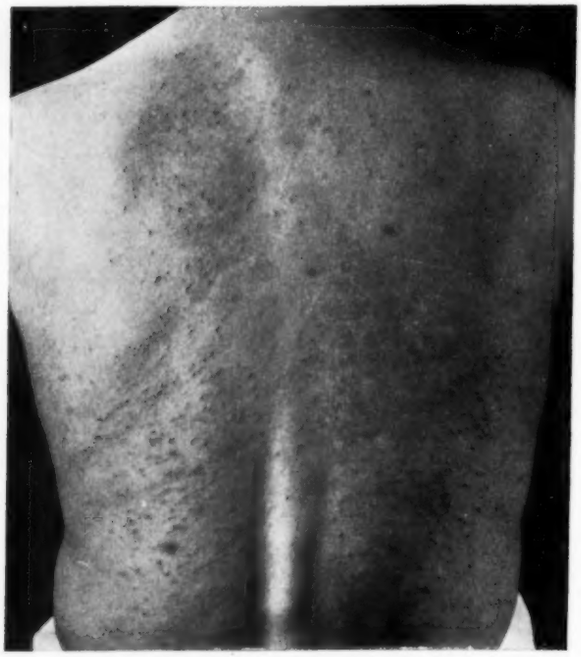

FIG. 5. Appearance of back after onset of xanthomatosis.

Assays of certain coagulation factors were performed in the tenth month of jaundice, and at a time when all medication had been discontinued for several weeks. One-stage prothrombin determinations revealed values slightly greater than 100 per cent. The true prothrombin assay was slightly greater than 400 per cent, as was the assay for proconvertin (factor VII). Assay for proaccelerin (factor V) was slightly over 300 per cent.

At the present time, ten months after the onset of his illness, the patient is asymptomatic except for severe pruritus which began in the sixth month of icterus. This symptom has proved refractory to the following drugs administered in appropriate dosage and for periods of time sufficient to demonstrate their ineffectiveness: phenobarbital, secobarbital, ephedrine, diphenhydramine, nitroglycerine, sodium dehydrocholate, ergotamine, intravenous procaine and prednisone. Trimeprazine (Temaril®) and other phenothiazine derivatives were withheld because of their chemical similarity to chlorpromazine. Testosterone therapy has afforded slight relief for brief periods. In an attempt to lower the serum cholesterol, a course of triparanol (MER 29®) was administered in dosage of 250 mg. daily for five weeks. There was no appreciable change in serum cholesterol. Currently, the patient is out of the hospital and is attempting to resume work.

COMMENTS

It has been stated that in approximately 25 per cent of patients treated with chlorpromazine, some evidence of hepatic dysfunction appears [*1*]. This abnormality is most often asymptomatic

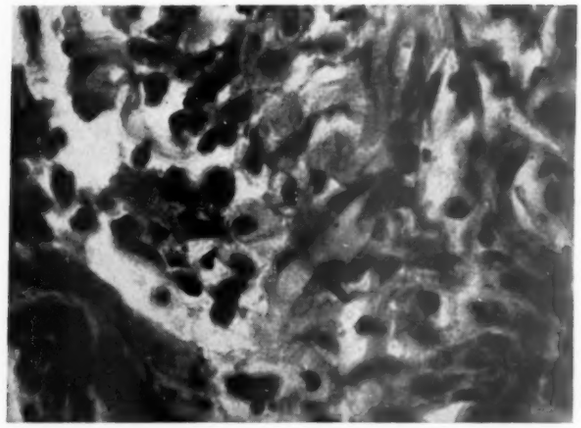

FIG. 6. Biopsy specimen of the skin (chest) showing histocytes with foamy cytoplasm characteristic of xanthoma.

and may even disappear with continued administration of the drug. In such instances it is detectable only through the demonstration of abnormalities in liver function tests, usually in the form of bromsulphalein retention and elevation of serum alkaline phosphatase and cholesterol. In approximately 1 per cent of the patients, jaundice appears but is usually of short duration [*2*]. The long-term prognosis in these patients has been considered to be benign [*3*], but detailed clinical, laboratory and histologic follow-up in some of them has pointed out the need for reserved opinion in this regard [*4*]. A rare fatality during the acute phase of jaundice has been noted [*5–7*]. In approximately 10 per cent of the patients, chloropromazine hepatitis lasts longer than three months [*8*] and prolonged jaundice continuing over a period of many months has been reported [*8–13*].

More severe and prolonged reactions associated with lipid disturbances have been noted in very few instances. In a patient treated with chlorpromazine, Stacey and others [*12*] noted the appearance of xanthelasma which lasted 197 days, but was followed by full recovery. Read and Sherlock [*11*] described four patients with jaundice which lasted from seven to thirty months. The serum cholesterol values were over 1,000 mg. per 100 ml. in all of these patients. In one of the four generalized xanthomatosis developed and portal hypertension was thought to be developing. Beattie and co-workers [*10*] observed a patient with chlorpromazine jaundice for eight months. At the end of this time no indication of remission had appeared and the serum cholesterol was 2,200 mg. per 100 ml., the serum alkaline phosphatase 59.4 King-Arm-

TABLE III

SUMMARY OF CASES OF CHRONIC HEPATIC DYSFUNCTION WITH XANTHOMATOSIS DUE TO CHLORPROMAZINE THERAPY

Authors	Duration of Jaundice	Serum Lipid Abnormalities	Evidence of Xanthomatosis	Outcome
Stacey et al. [*12*]	197 days	Not stated	Xanthelasma	Complete recovery
Beattie et al. [*10*]	240+ days	Total cholesterol 2,200 mg. %	+	Still icteric after 8 mo.
Read, Sherlock [*11*]	30 mo.	Total cholesterol 1,620 mg. %	+	Portal hypertension
Myers et al. [*13*]	23 mo.	Total lipids 9,000 mg. %; total cholesterol 2,500 mg. %; phospholipids 4,800 mg. %	+	Portal hypertension, biliary cirrhosis
Kohn, Myerson	300+ days	Total lipids 6,800 mg. %; total cholesterol 1,765 mg. %; phospholipids 3,450 mg. %	+	Persistent jaundice and hepatosplenomegaly

strong units. Cutaneous xanthomas were present. They employed the term "hepatohypercholesterolemic cirrhosis" in describing this syndrome. A well documented similar case was reported by Myers and his associates [*13*]. The duration of jaundice in their patient was twenty-three months; hepatosplenomegaly was present and there was generalized xanthomatosis. A serum total lipid level of over 9,000 mg. per 100 ml. was found; of this, the serum cholesterol accounted for 2,500 mg. The presence of portal hypertension was proved in this case by catheterization of the hepatic vein. The outcome in this patient was still uncertain, but the prognosis was considered to be poor. As in the present patient, Myers and his associates demonstrated the presence of markedly elevated levels of circulating coagulation factors, including prothrombin, proconvertin and proaccelerin. In addition, studies with acetate-l-C^{14} indicated a greatly enhanced hepatic production of cholesterol and phospholipid, a finding possibly calling for revision of the concept that in xanthomatous liver disease the observed hyperlipemic state results from retention of substances secondary to inadequate flow of bile.

A tabulation of cases characterized by chronic liver abnormalities with xanthomatosis following administration of chlorpromazine is given in Table III. This group of cases is quite similar to the syndrome variously described as xanthomatous biliary cirrhosis, primary biliary cirrhosis or hepatohypercholesterolemic cirrhosis.

Thannhauser and Magendantz [*14*] delineated the five outstanding characteristics of this disorder. These included (1) the presence of skin xanthomas, (2) hepatosplenomegaly, (3) obstructive jaundice which lasts for years, (4) extremely high values for serum total cholesterol and lecithin, and (5) absence of a milky serum. Cinchophen and arsphenamine have been incriminated in the evolution of a picture indistinguishable from xanthomatous biliary cirrhosis [*15–18*]. On the basis of the evidence presented in this report, it is likely that chlorpromazine should be added to this group of drugs.

In speaking of chronic liver disorders following the use of certain drugs, Sherlock [*19*] recently pointed out certain similarities with and differences from the idiopathic type of xanthomatous biliary cirrhosis. Although obstructive jaundice, relative well-being, pruritus, very high serum cholesterol levels and xanthomas are common to both, certain clinical and histologic features distinguish one from the other. The outcome in the primary disorder is uniformly fatal, while in the drug-induced disorder recovery takes place. Although stressing these differences, Sherlock concedes that an unknown number of cases regarded as instances of primary biliary cirrhosis may indeed be due to unsuspected drug injury.

Although emphasis has been placed upon the effect of chlorpromazine upon the smaller biliary radicles, little has been noted of the possible hepatocellular effect. Recently, this has been reevaluated, with the conclusion that in certain cases there is significant hepatocellular necrosis [*20*]. The marked elevations in serum SGPT and SGOT noted in this case would tend to support this concept.

The prompt improvement in certain abnormalities of liver function observed following institution of T-tube drainage of the common duct has been noted before in cases of chlor-

promazine jaundice [*21*], as well as in a few cases of primary biliary cirrhosis [*19*]. The explanation for this interesting phenomenon is unknown. Menguy and his associates [*22*] in experimental work on dogs, demonstrated that chlorpromazine may have some extrahepatic effect upon the biliary tree, particularly upon the biliary sphincteric mechanism and upon intraductal pressure within the common duct. However, this effect is evanescent and would be inadequate to explain the improvement in itching and jaundice observed following surgery in subjects from whom chlorpromazine therapy had been withdrawn for some time.

The prognosis in this disorder cannot be stated at this time. As in the four cases of xanthomatous liver disease reported in the literature, the ultimate outcome in the case described herein is unknown. Despite the view that complete recovery is the rule in this type of hepatic dysfunction [*19*], study of these cases does not seem to warrant this conclusion.

Treatment for this condition is centered upon the only disturbing symptom, namely pruritus. This usually proves refractory to a wide variety of drugs. Recently, norethandrolone has been noted to be effective [*11,19*]. Although the administration of corticosteroids and their variants has been suggested in the treatment of chlorpromazine jaundice [*23*], the use of these drugs in the protracted form of the disease described in this report has been uniformly unsuccessful.

SUMMARY

A case of chlorpromazine-induced jaundice, progressing to a chronic hepatic disorder characterized by a marked disturbance of lipid metabolism, with formation of xanthomas and resembling xanthomatous biliary cirrhosis, is presented. Markedly elevated levels of prothrombin, proconvertin and proaccelerin were also present.

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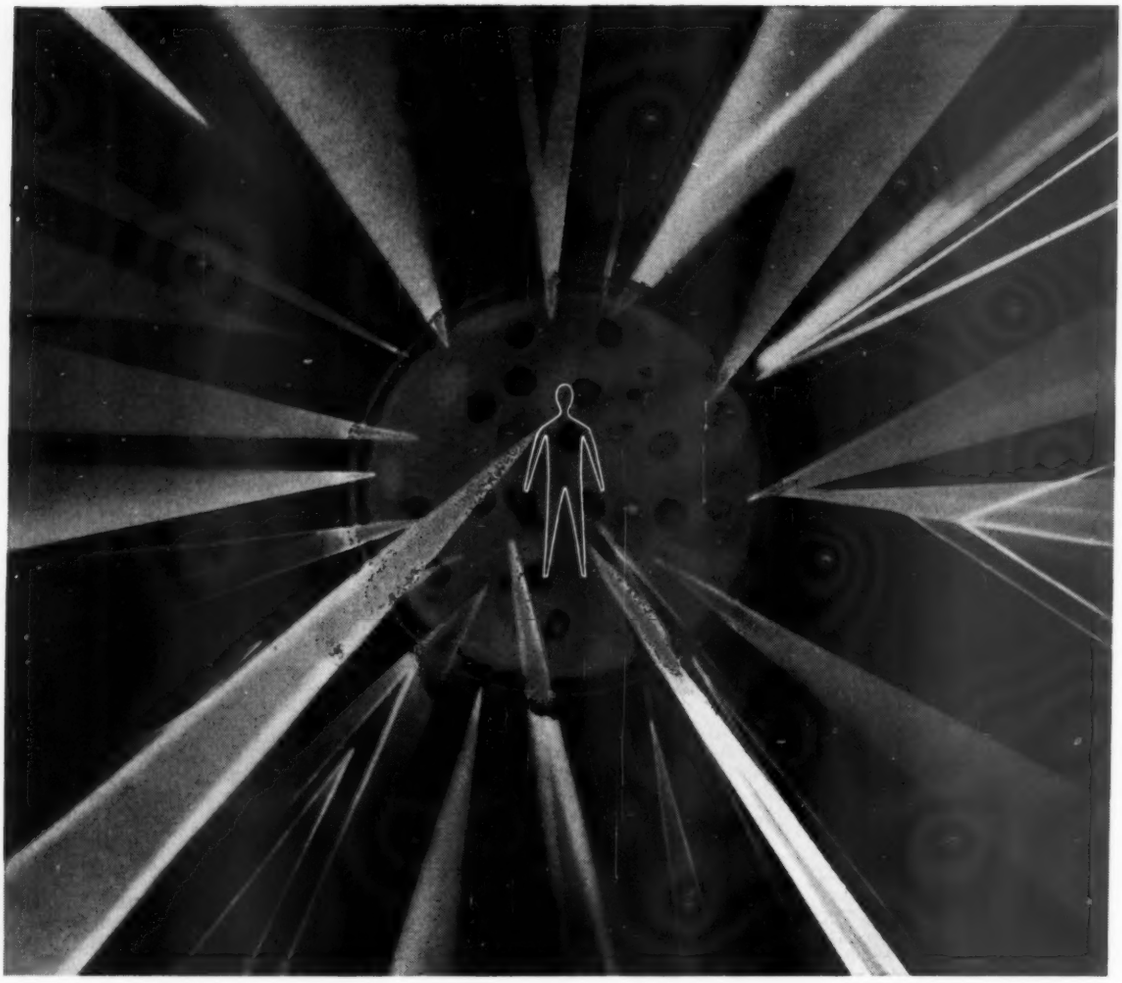

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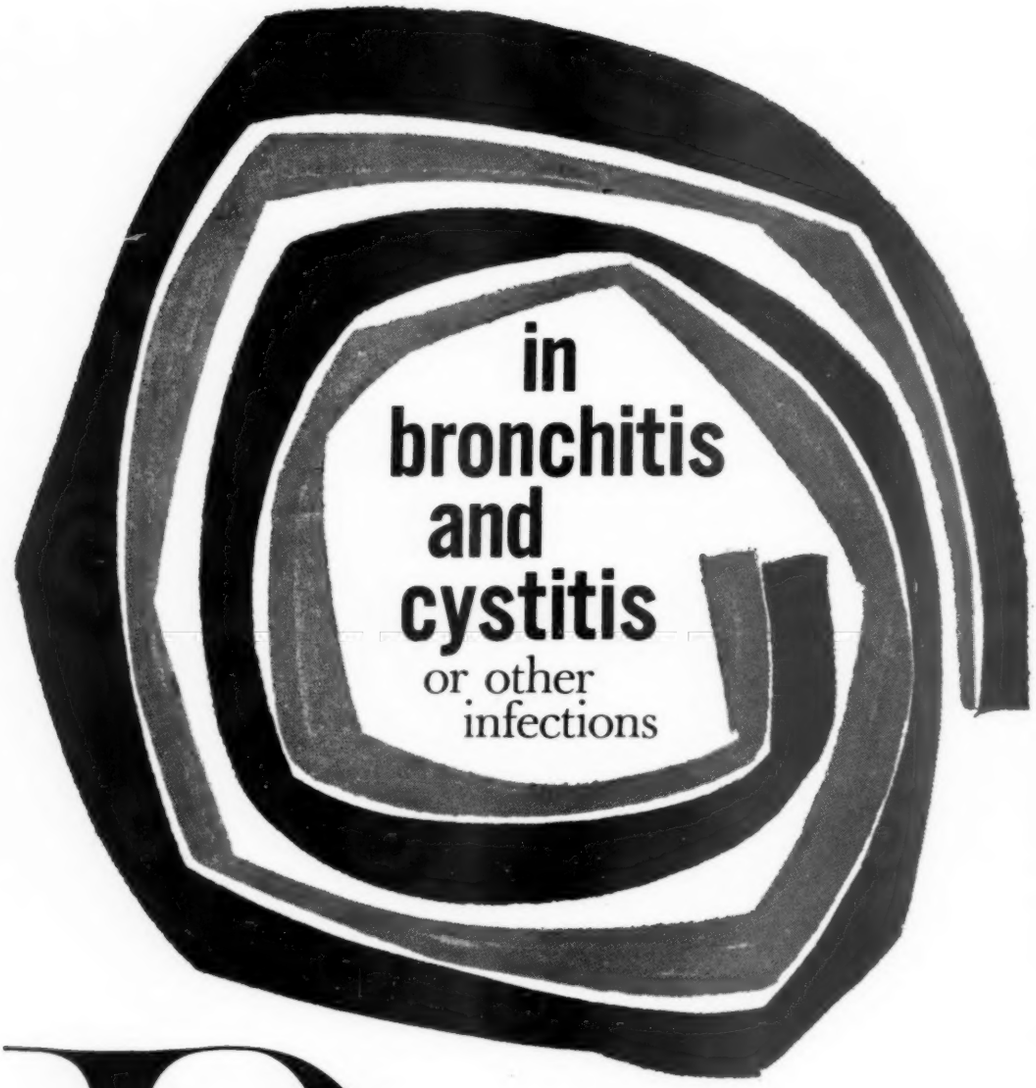

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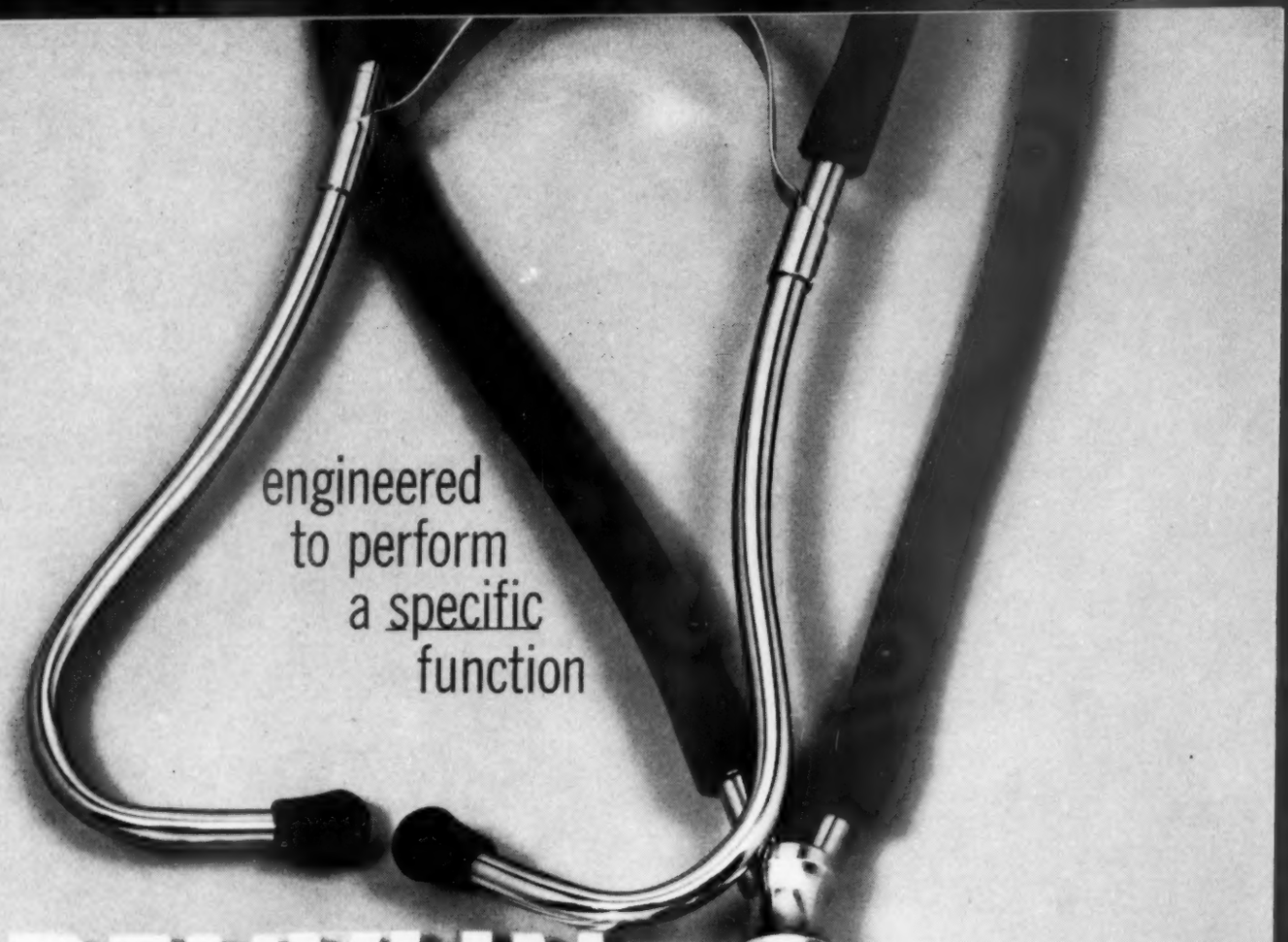

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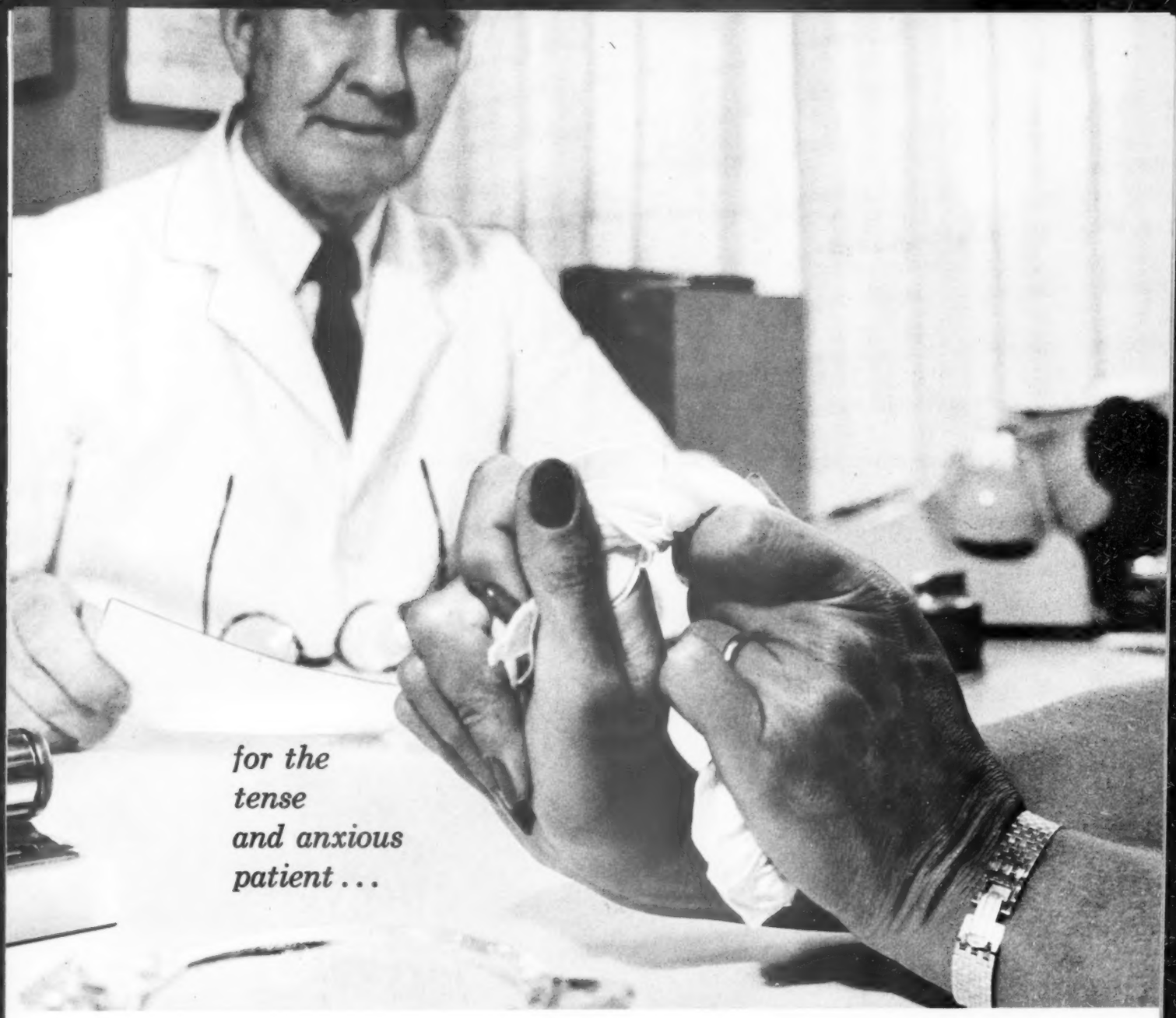

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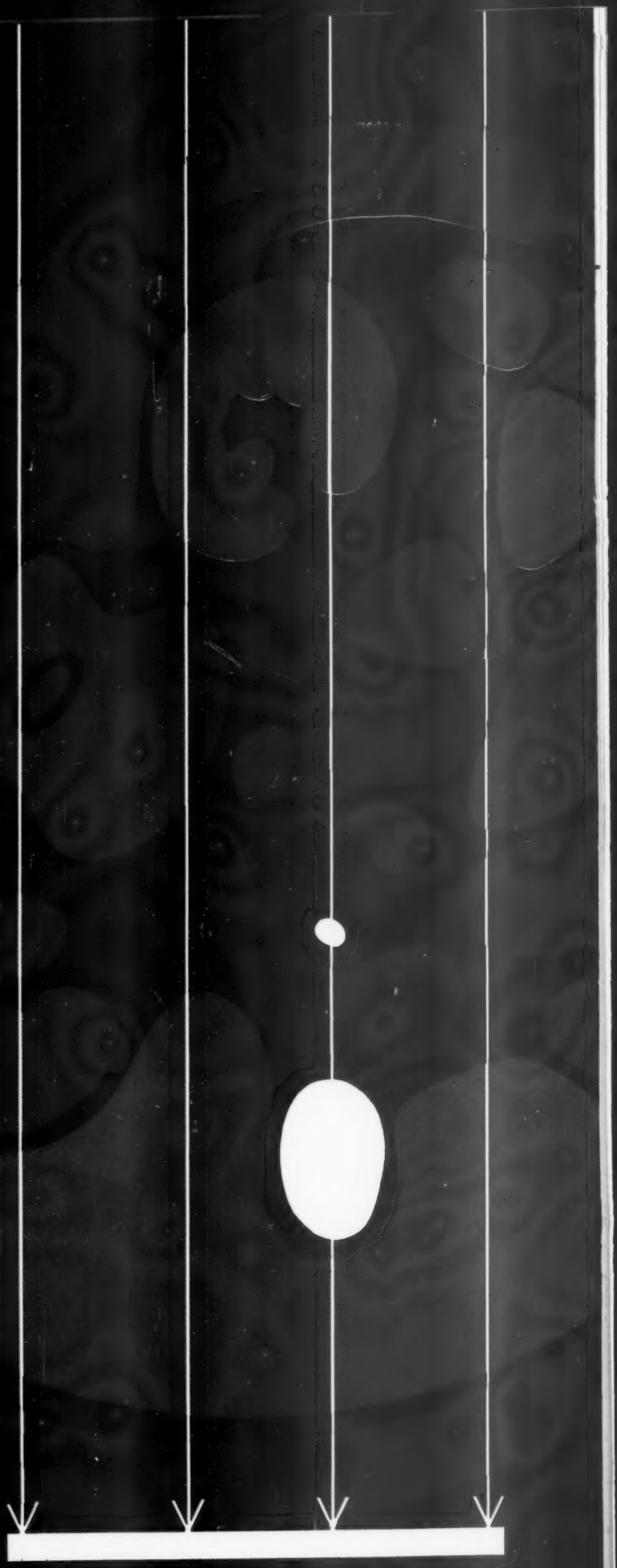

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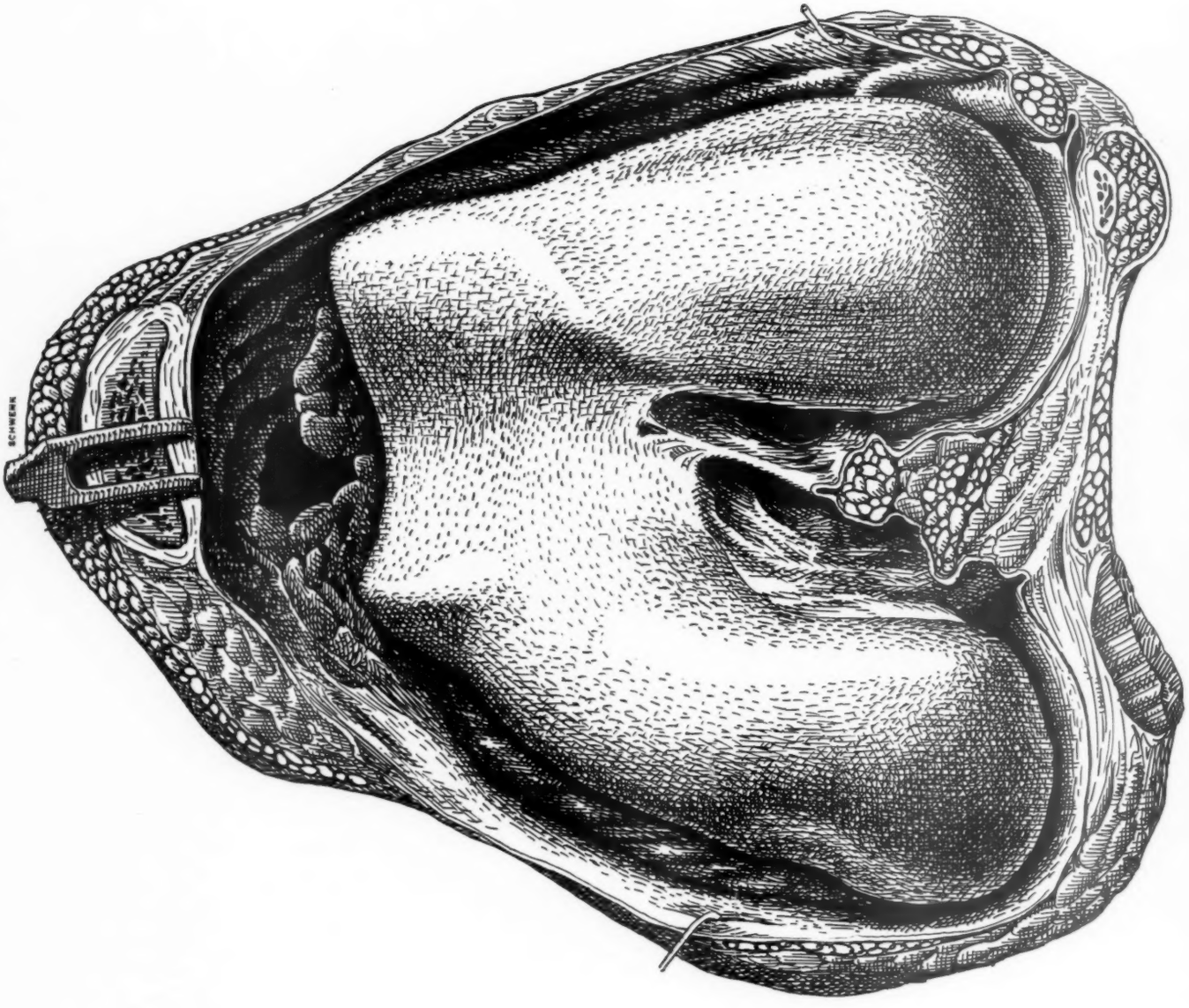

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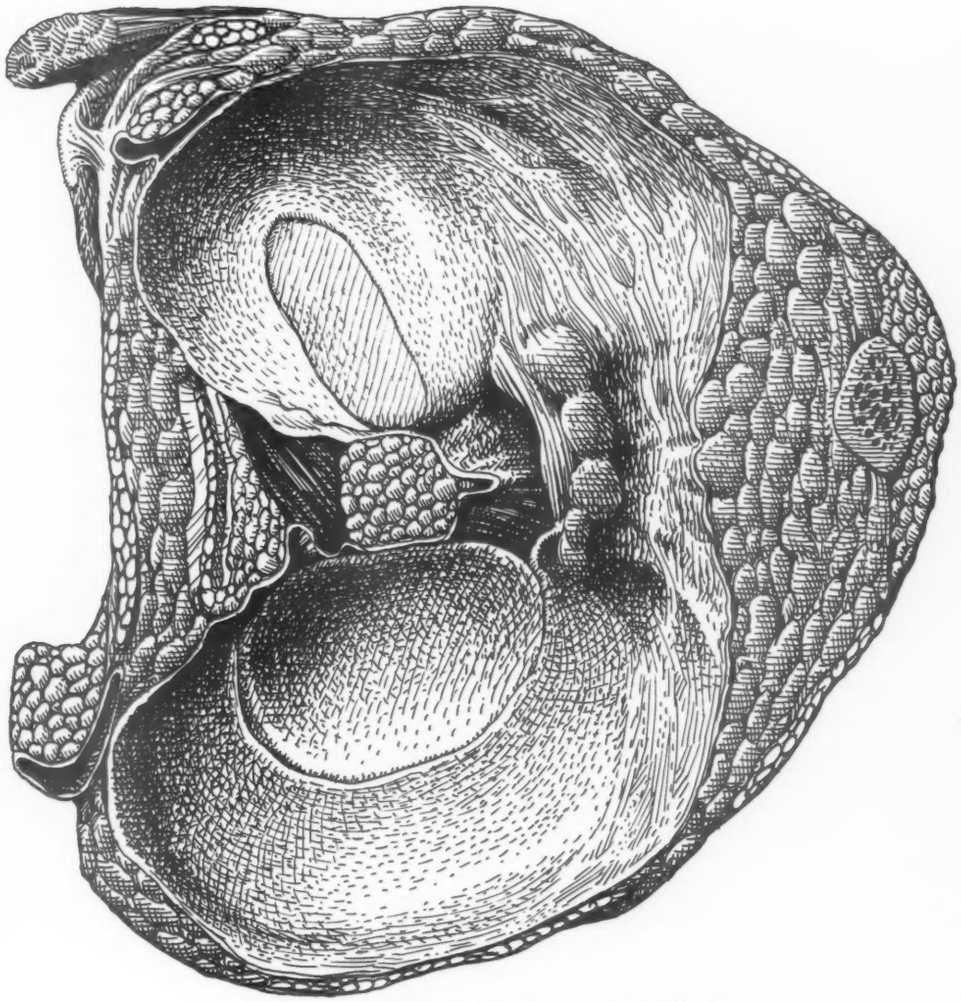

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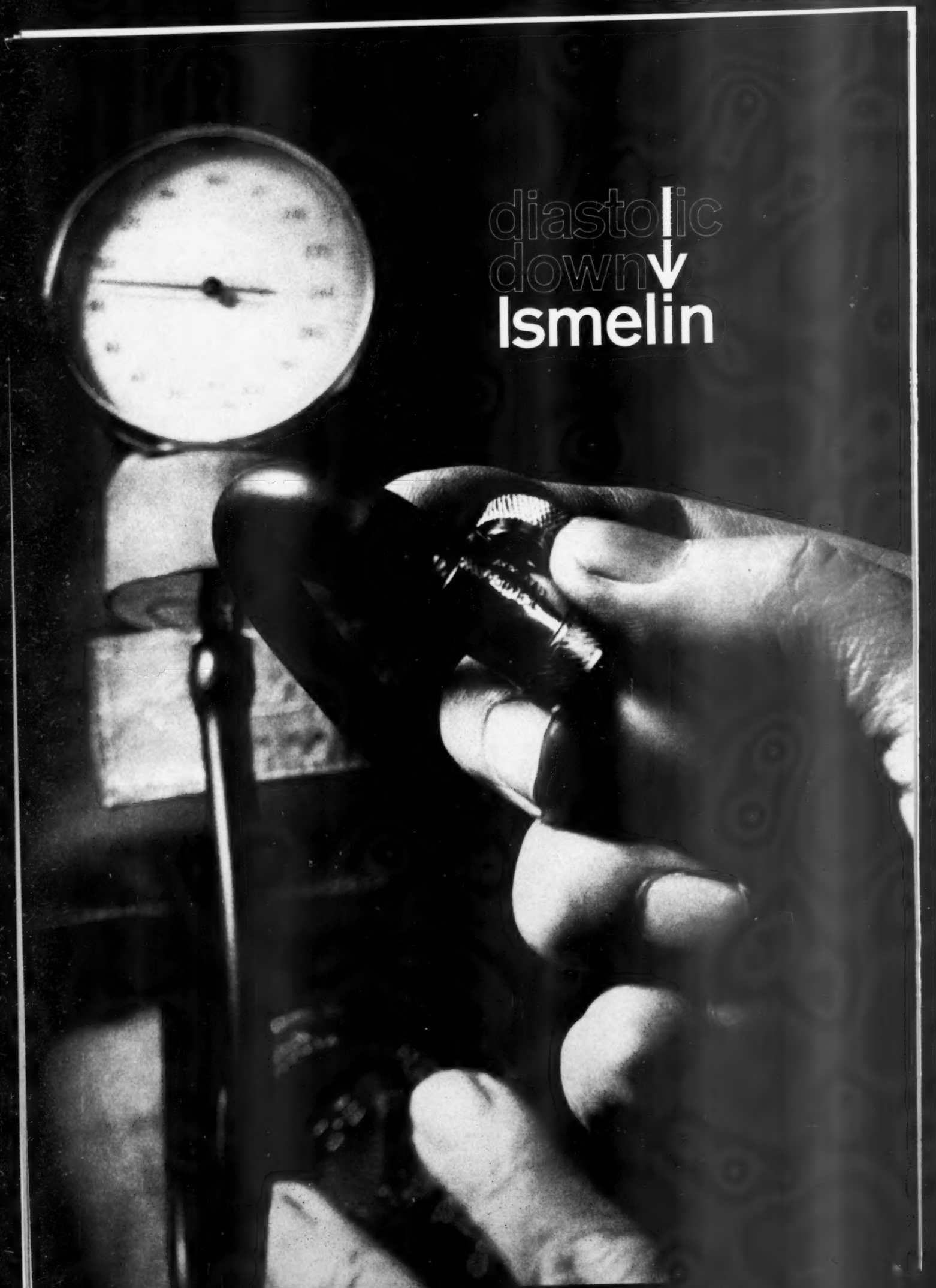
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Elevated diastolic pressure of "crucial importance."[2] Increased peripheral resistance, as reflected by elevation of diastolic blood pressure, has been described as: "The single most important factor in the production of the type of arterial hypertension with which the physician is usually concerned..."[2]

Ismelin, through its unique action at the nerve-arteriole junction, dilates the arterioles, thereby reducing peripheral resistance. The result is often a marked decrease in diastolic pressure, as confirmed repeatedly by clinical observation.

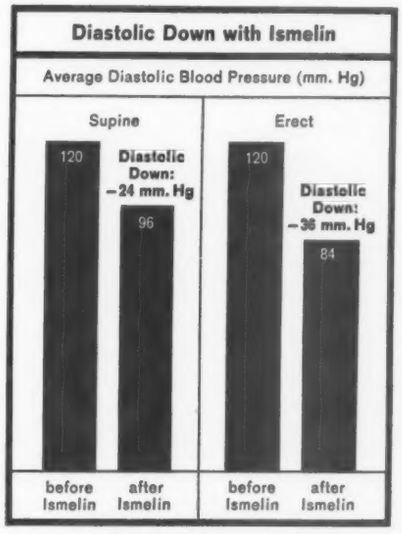
Ismelin lowers diastolic pressure after other treatments fail. Riven and Hall[3] studied Ismelin in 21 male hypertensive patients ranging in age from 30 to 69 years. Most patients were hospitalized initially, and most were treated with other antihypertensive drugs. Before treatment with Ismelin, all patients had diastolic pressures (supine and erect) of at least 110 mm. Hg "despite other antihypertensive therapy including ganglionic blocking agents."

All 21 patients responded to Ismelin* with "...a decrease in systolic and diastolic pressure in both supine and standing positions..."[3]

*When therapy with Ismelin began, mecamylamine was discontinued in 7 patients receiving it.

Advantages of Ismelin for your hypertensive patients

- Almost all forms of moderate to severe hypertension (including malignant hypertension and many cases of renal hypertension) can be managed with Ismelin — alone or in combination with other antihypertensive agents.
- Ismelin brings blood pressure down in many persons refractory to other antihypertensive agents.
- Ismelin lowers blood pressure in many patients who cannot be treated effectively with other potent agents because they do not tolerate the side effects.
- Patients need take Ismelin but once a day.



(Adapted from Riven and Hall[3])

- Most patients have been treated with Ismelin for prolonged periods without developing tolerance to it (although instances of tolerance have been reported).
- Smooth absorption of Ismelin results in predictable blood pressure responses.

For complete information about Ismelin (including dosage, cautions, and side effects), see current Physicians' Desk Reference or write CIBA, Summit, N. J.

Supplied: Tablets, 10 mg. (pale yellow, scored) and 25 mg. (white, scored)

References: 1. Brest, A. N. Novack, P., and Moyer, J. H.: To be published. **2.** Harrison, T.R., Adams, R.D., Bennett, I.L.Jr., Resnick, W. H., Thorn, G. W., and Wintrobe, M. M. (Editors): **Principles of Internal Medicine,** The Blakiston Division, McGraw-Hill Book Company, Inc., New York, 1958, p. 1321. **3.** Riven, S. S., and Hall, W.: South. M. J. 54:673 (June) 1961.

2/2986 MB

ISMELIN® sulfate (guanethidine sulfate CIBA)

diastolic down **Ismelin®**

CIBA Summit, New Jersey

new Renese®
POLYTHIAZIDE

1 mg. 2 mg. 4 mg.

A MORE CLINICALLY USEFUL
DIURETIC/ANTIHYPERTENSIVE

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broad benefit
clinically confirmed
convenient control
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dependable diuresis
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marked micturition
notable natruresis
orally optimal
peak potency
prolonged performance
reliable response
significant saluresis
tested toleration
unsurpassed utility
valuable versatility

"active antihypertensive" – RENESE is a highly effective antihypertensive agent when used alone or concomitantly with other agents such as rauwolfia or blocking agents. Excellent-to-good clinical response has been reported in 145 out of 180 patients with hypertension alone and in 109 out of 128 patients with hypertension and associated congestive heart failure. Some of these patients had been refractory to previous therapy.

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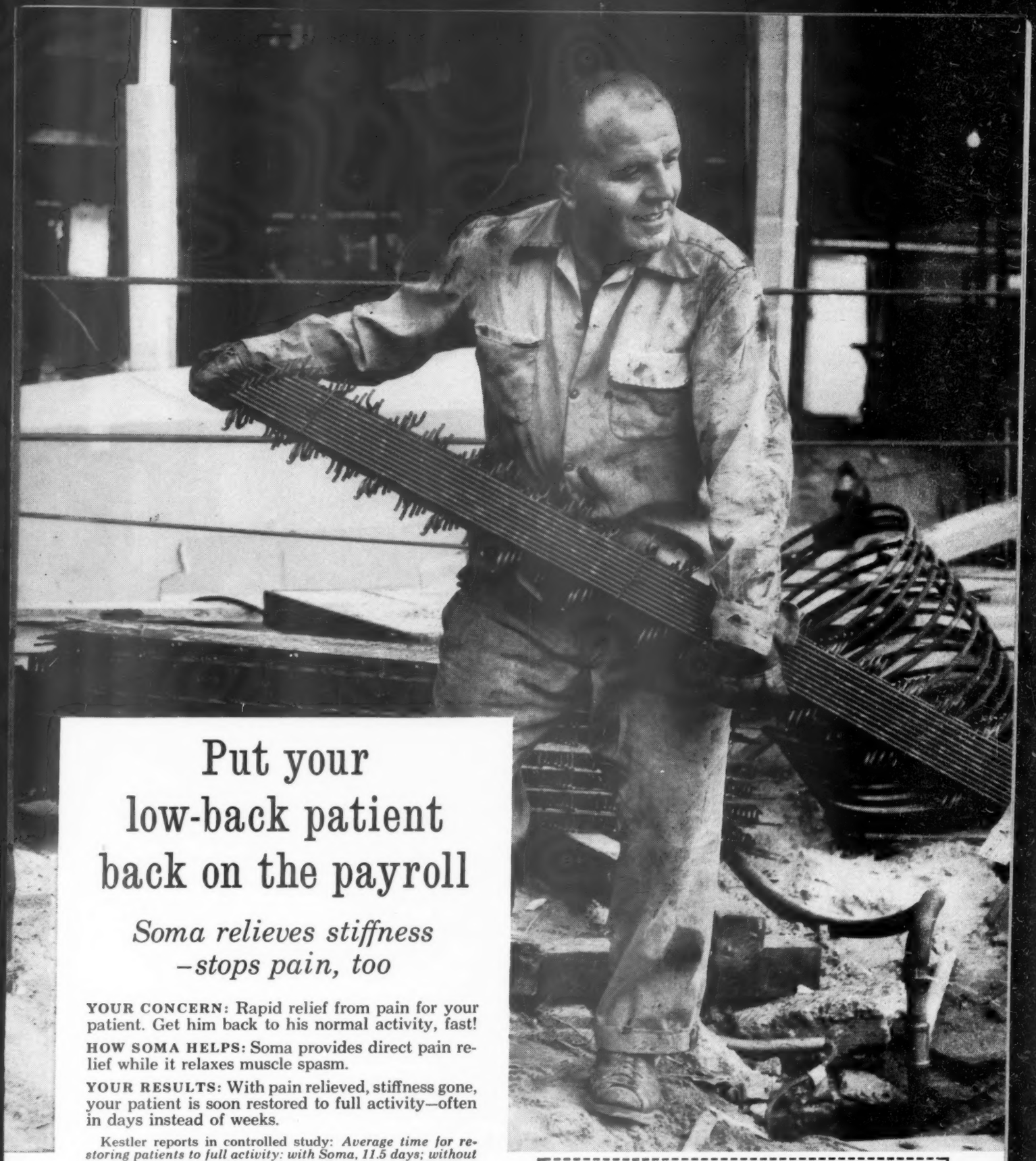
FOR PRODUCT INFORMATION TURN TO PAGE 126



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YOUR RESULTS: With pain relieved, stiffness gone, your patient is soon restored to full activity—often in days instead of weeks.

Kestler reports in controlled study: *Average time for restoring patients to full activity: with Soma, 11.5 days; without Soma, 41 days. (J.A.M.A. Vol. 172, No. 18, April 30, 1960.)*

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The muscle relaxant with an independent pain-relieving action

SOMA®

(carisoprodol, Wallace)

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Type of practice_____

a pair of cardiac patients:

both are free of pain—but only one is on

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swift, sure analgesia normally unmarred by nausea and vomiting

DILAUDID provides unexcelled analgesia in acute cardiovascular conditions. Onset of relief from pain is almost immediate. The high therapeutic ratio of DILAUDID is commonly reflected by lack of nausea and vomiting—and marked freedom from other side-effects such as dizziness and somnolence.

▲ by mouth ▲ by needle ▲ by rectum

2 mg., 3 mg., and 4 mg.

May be habit forming—usual precautions should be observed as with other opiate analgesics.

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for functional disorders of the menopause

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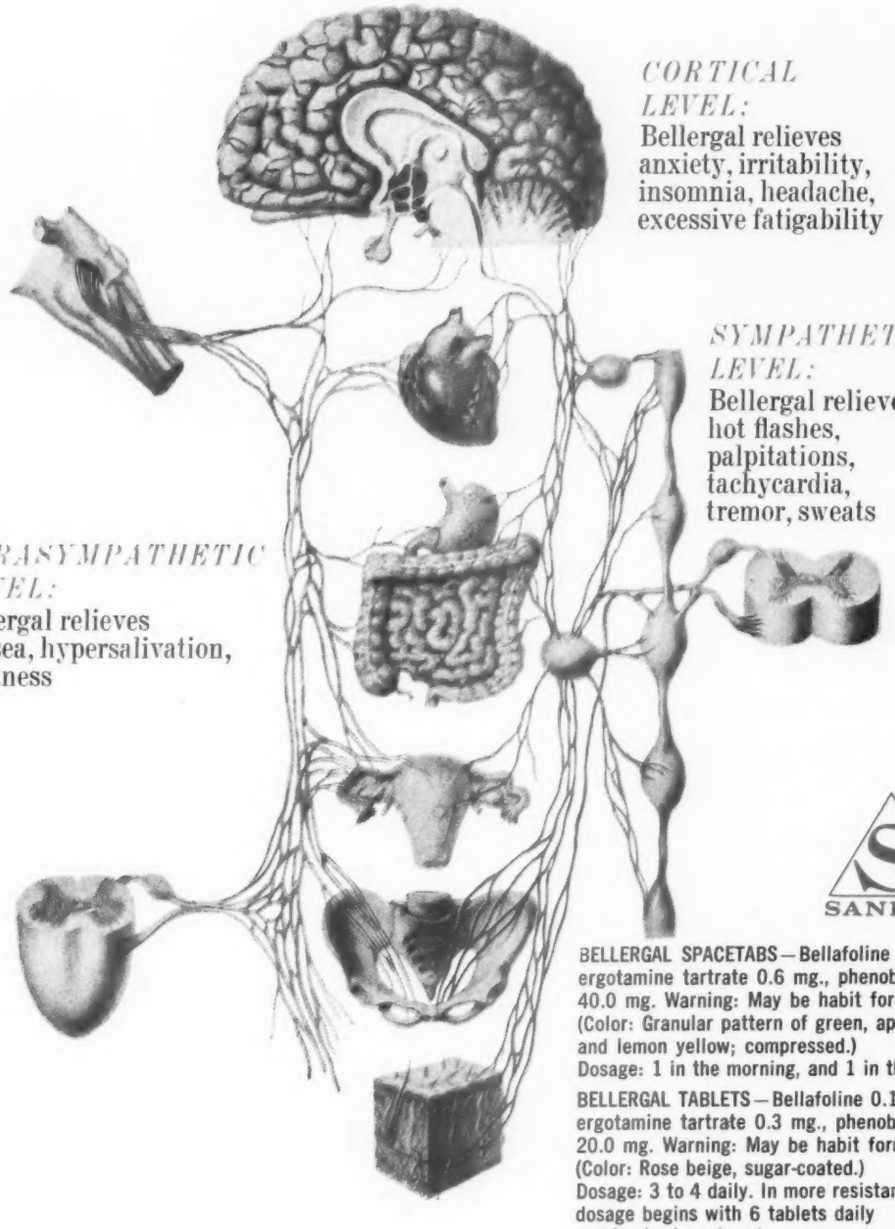
stabilizes the entire autonomic nervous system

(without disturbing endocrine balance)



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Bellergal relieves anxiety, irritability, insomnia, headache, excessive fatigability

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Bellergal relieves hot flashes, palpitations, tachycardia, tremor, sweats

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BELLERGAL SPACETABS—Bellafoline 0.2 mg., ergotamine tartrate 0.6 mg., phenobarbital 40.0 mg. Warning: May be habit forming. (Color: Granular pattern of green, apricot and lemon yellow; compressed.)
Dosage: 1 in the morning, and 1 in the evening.

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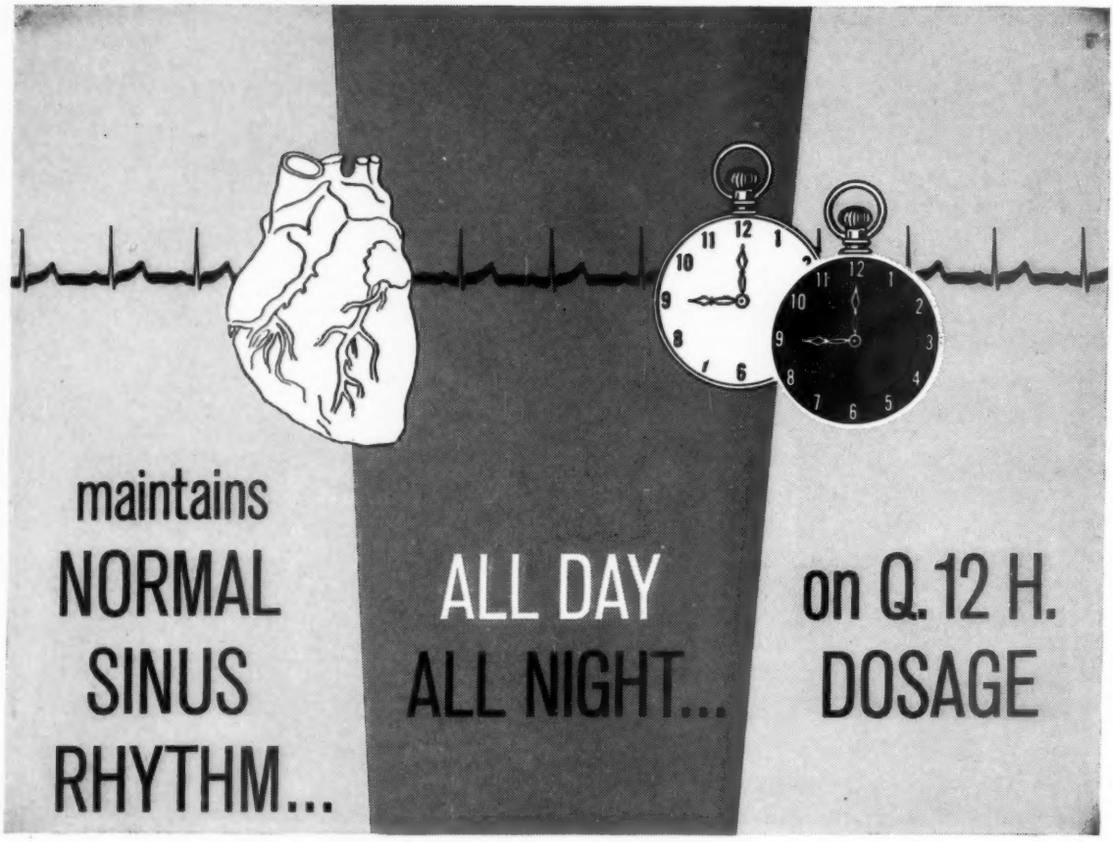
Dosage: 3 to 4 daily. In more resistant cases, dosage begins with 6 tablets daily and is slowly reduced.



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IN CARDIAC ARRHYTHMIAS[1-10]

Maximum efficacy: maintains effective quinidine blood levels all day, all night. **Better tolerated:** because quinidine gluconate is 10 times as soluble as the sulfate, and only part of daily Dura-Tab dosage contacts gastric mucosa. **Maximum convenience:** given q. 12 h.—no night dosage needed.

DOSAGE: for conversion of auricular fibrillation to normal sinus rhythm, in most cases, 2 Dura-Tabs 3 or 4 times a day, for 2 to 3 days; longer periods are required in some patients. **For maintenance,** 2 Dura-Tabs q. 12 h. in most patients . . . Bottles of 30, 100 and 250 Quinaglute Dura-Tabs.

For SAMPLES and complete literature[1-10] giving indications, cautions, etc., write

REFER TO PDR Page 821

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during pregnancy...
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50/1000 Tablets

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Also available: ESIDRIX-K 25/500 Tablets (off-white, coated), each containing 25 mg. Esidrix and 500 mg. potassium chloride. ESIDRIX Tablets, 50 mg. (yellow, scored) and 25 mg. (pink, scored).

For complete information about Esidrix and Esidrix-K (including dosage, cautions, and side effects), see current Physicians' Desk Reference or write CIBA, Summit, N. J.

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One daily dose controls edema and hypertension around the clock

Every tablet delivers 24 hours' continuous thiazide action

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(Methyclothiazide, Abbott) Supplied in 2.5 and 5 mg. grooved tablets.

Enduron's duration of action is neatly matched to the 24-hour day. This 24-hour duration permits an ideal dosage: "*Once* a day, *every* day." Easy for you to supervise, and handy for your patients, with fewer forgotten doses, and no gaps in your therapy.

Diuretic response is smooth and continuous. Patients continue to eliminate excess sodium at a rate well above control levels throughout the entire 24-hour period.[1]

POTASSIUM CONTROL SIMPLIFIED

Potassium depletion is rare. Enduron's *single* daily dose causes but a *single* temporary peak of potassium loss.

Moreover, Enduron's effect on potassium has upper limits. Thus doubling the single dose from 5 to 10 mg. approximately doubles the output of sodium; yet under this same condition, potassium output increases little or not at all.[2]

Use Enduron to treat the edema of congestive heart failure, the nephrotic syndrome, hepatic cirrhosis, premenstrual tension, or steroid therapy. Enduron also demonstrates significant antihypertensive effect.[1,3] You may use it as a primary measure for mild to moderate hypertension, or as an adjunct in more severe cases.

1. Ford, R. V. Current Therap. Res., 2:422-430, Sept., 1960.
2. Fuchs, Morton, and Seller, Robert H., to be published.
3. Bryant, J. M., et al., Current Therap. Res., 3:1-4, Jan., 1961.

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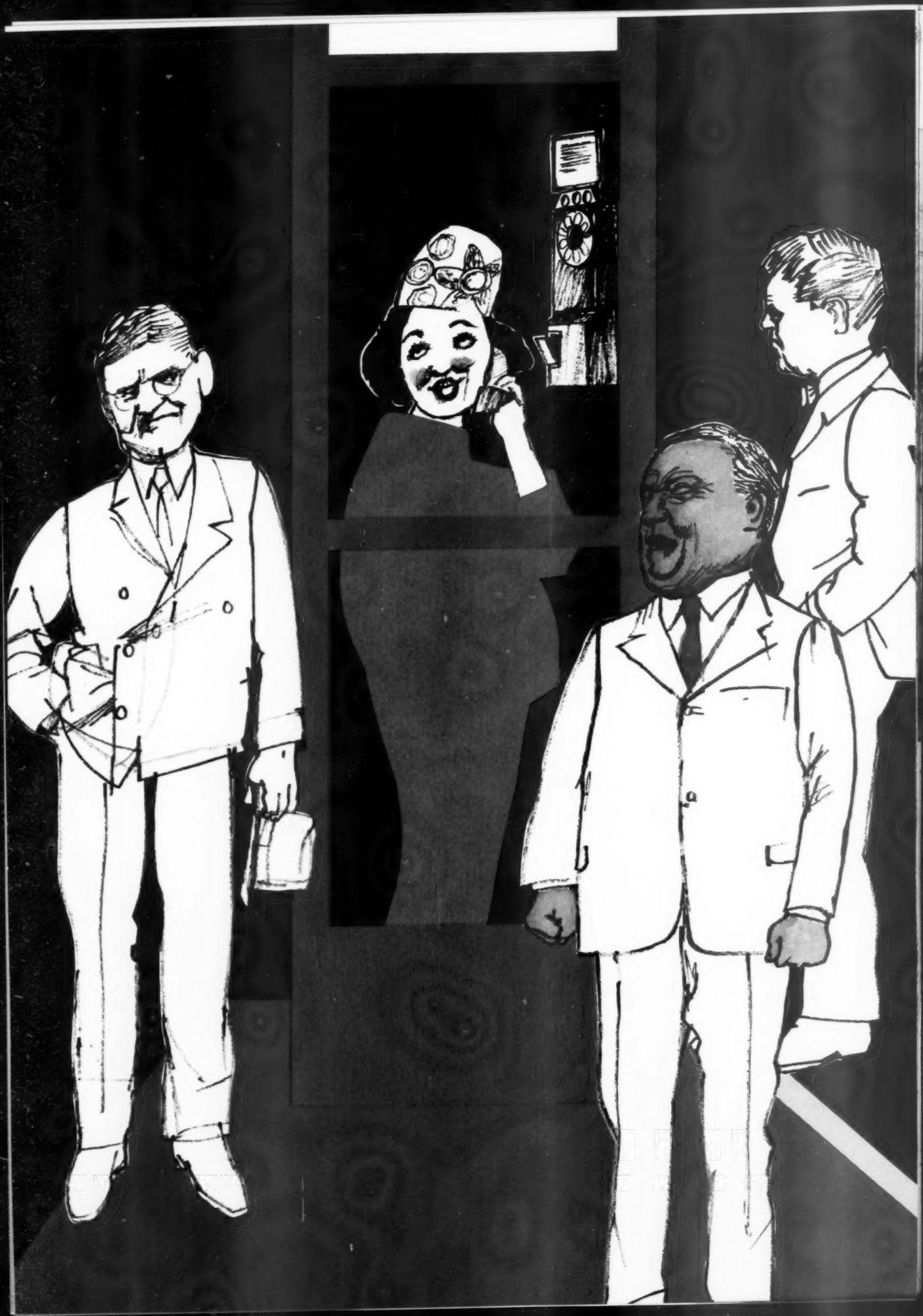

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—keep it under control with
Enduronyl

Announcing a once-a-day thiazide/rauwolfia antihypertensive

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Yes, just *once* daily is the dose for hypertension. Blood pressure starts down steadily: improvement usually is substantial within 10 days. Further reduction may continue over following weeks. At the same time, excess sodium and water are consistently eliminated.

Giving Enduronyl just once a day means fewer forgotten doses. A smoothly sustained therapeutic response, too.

On the other hand, single doses produce only one low, brief peak of potassium excretion. Hence one-a-day dosage means reduced chance of potassium depletion, since there's but one daily boost to the patient's potassium outgo.

WHAT IS ENDURONYL?

Enduronyl combines two well-established antihypertensive agents: (1) Enduron, Abbott's long-acting thiazide diuretic, and (2) Harmonyl, a rauwolfia derivative of low side effects. Together they provide greater hypotensive action than with either alone.

Enduronyl is supplied in two formulas, to cover a wide range of cases from mild to moderately severe hypertension. Would you like the literature? Write Abbott, North Chicago, Ill.

Supplied:
Enduronyl—(5 mg. Enduron, and 0.25 mg. Harmonyl)
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- ★ **Electron Microscopy of the β Cell**
- ★ **Immunologic Aspects of Diabetes**
- ★ **The Production of a Diabetic State by Immunologic Technics**
- ★ **The Prediabetic State**
- ★ **Critique of Oral Antidiabetic Therapy**
- ★ **The Microscopy and Chemistry of the Glomerulosclerotic Lesion**

Contributors include:

GEORGE YERGANIAN, M.D., *Boston Children's Hospital, Boston, Mass.*
HANS MEIER, M.D., *Jackson Memorial Laboratory, Bar Harbor, Maine*
RACHMIEL LEVINE, M.D., *New York Medical College, New York, N. Y.*
THEODORE B. VAN ITALLIE, M.D., *St. Luke's Hospital, New York, N. Y.*
PAUL LACY, M.D., *Washington University, St. Louis, Mo.*
SOLOMON A. BERSON, M.D. and ROSALYN S. YALOW, M.D., *Veterans Administration Hospital, Bronx, N. Y.*
PETER WRIGHT, M.D., *Northwestern University School of Medicine, Chicago, Ill.*
JEROME CONN, M.D., *University of Michigan School of Medicine, Ann Arbor, Mich.*
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Prompt relief... early recovery—In low-back cases, or for patients with inflammatory or traumatic musculoskeletal complaints, RELA offers the promise of prompt relief and early recovery. In a study[1] of 212 conservatively treated low-back patients, 106 treated also with carisoprodol [RELA] were 'back in action' in one-fourth the time it took the conventionally treated group. RELA speeds recovery by a combination of effects—analgesic and muscle relaxant—to reduce spasm and tension, relieve pain, restore mobility. Undesirable effects have been minimal.

SUPPLIED: Bottles of 30, 350 mg. tablets. **REFERENCE:** 1. Kestler, O. C.: J.A.M.A. 172:2039 (April 30) 1960. **For complete details, consult latest Schering literature available from your Schering Representative or the Medical Services Dept., Schering Corporation, Bloomfield, New Jersey.**

H-406

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brand of carisoprodol

Schering

helps
you "reach"
the depressed
office
patient

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provides remission of depression—smoothly, gradually, without "jarring" □ notably low incidence of serious complications or side effects □ convenience of once-a-day dosage

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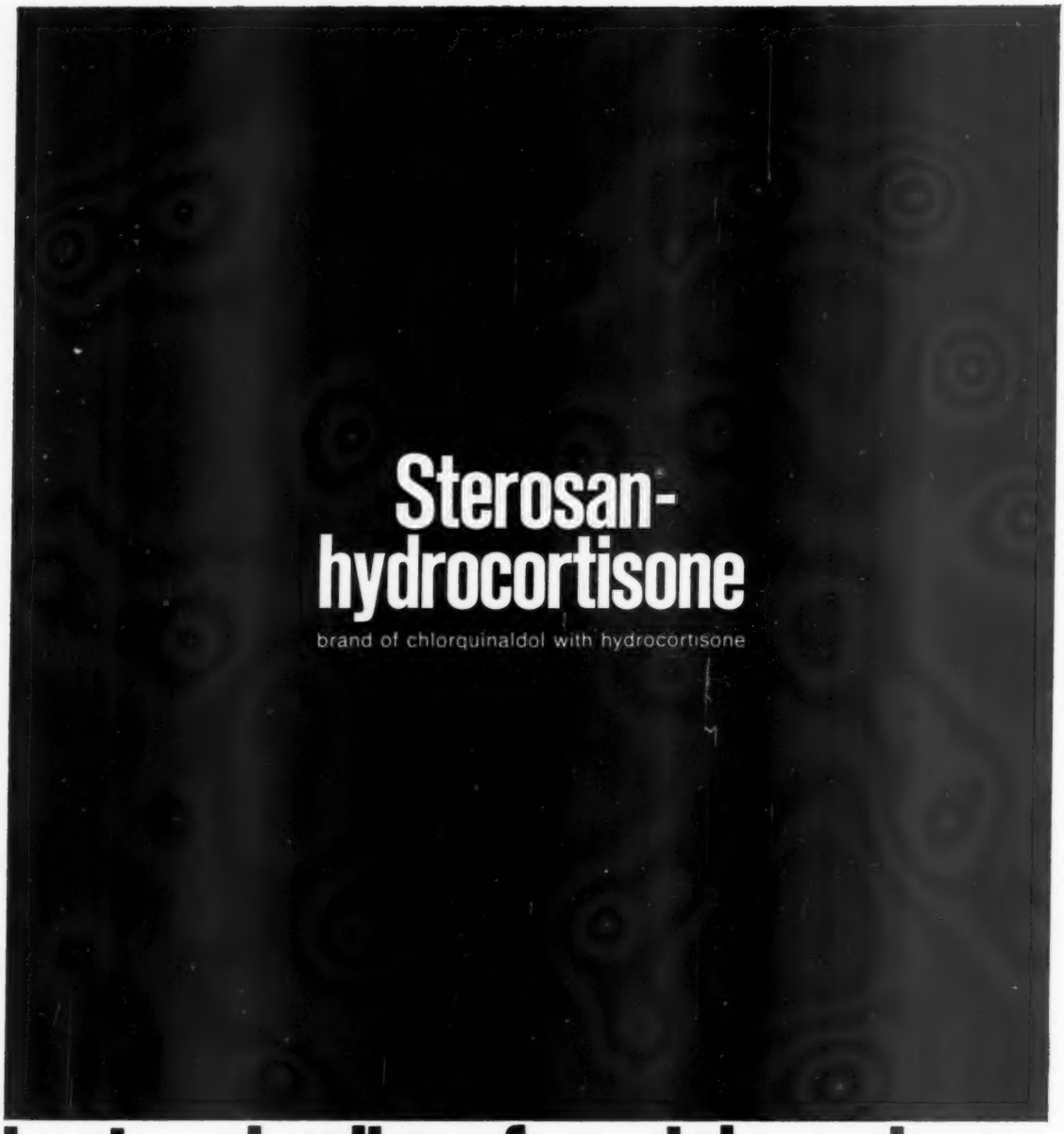
restores
the will
to
improve

In Brief Niamid, brand of nialamide, is 1-(2-[benzylcarbamyl] ethyl)-2-isonicotinyl-hydrazine, a well-tolerated antidepressant that may correct or relieve depression on once-a-day dosage. **Indications:** Depressive syndromes of varying degrees of severity may be responsive to Niamid including: involutional melancholia, postpartum depression, depressed phase of manic-depressive reaction, senile depression, reactive depression, schizophrenic reaction with depressive component, psychoneurotic depression. ■ In neurotic or psychotic patients, Niamid may normalize or favorably modify aberrant or excessive reactions and symptoms of depression such as: phobias, guilt feelings, dejection, feeling of inadequacy, discouragement, worry, uneasiness, distrustfulness, hypochondriacal and nihilistic ideas, difficulty in concentration, insomnia, loss of energy or drive, indecision, hopelessness, helplessness, decreased functional activity, emotional and physical fatigue, irritableness, inability to rest or relax, sadness, anorexia and weight loss, and withdrawal from society. *In the withdrawn patient,* Niamid may elevate the mood so that there is increased activity, increased awareness and interest in surroundings, and increased participation in group activities. Appetite may be increased and there may be decreased fatigability. Lack of clinical response to other antidepressant therapy does not preclude a favorable response to Niamid. Relief of depression may also be evidenced by elimination or reduction of the need for somatic therapy, such as electroshock. *In patients suffering from depression associated with chronic illness,* Niamid may improve mental outlook, reduce the impact of pain, decrease the amounts of narcotics or analgesics needed, and improve appetite and well-being. *In patients with angina pectoris,* Niamid has been found to be a useful adjunct to management through reduction in frequency of attacks and pain. **Dosage:** Starting dosage is 75 to 100 mg. on a once-a-day or divided daily basis. This may subsequently be adjusted depending upon the tolerance and response. Responses to Niamid are not usually rapid, and revisions of dose should be withheld until at least a few days have elapsed at each level. Increments or decrements of 12½-25 mg. are generally sufficient. A daily dosage of 200 mg. is the maximum recommended for routine use. (As much as 450 mg. daily has been used in some patients.) **Side Effects:** Niamid, in clinical use, has been characterized by a significant lack of toxicity. It is generally well tolerated. Nervousness, restlessness, insomnia, hypomania, or mania, sometimes occur. Occasional headache, weakness, lethargy, vertigo, dryness of the mouth, blurred vision, increased perspiration, constipation, mild skin rash, mild leukopenia, and epigastric distress may be obviated or modified by reductions in dose. Effects due to monoamine oxidase inhibition persist for a substantial period following discontinuation of the drug. **Precautions and Contraindications:** Hepatic toxicity has not been reported in extensive clinical studies. However, if previous or concurrent liver disease is suspected, the possibility of hepatic reactions and liver function studies should be considered. ■ The suicidal patient is always in danger, and great care must be exercised to maintain all security precautions. The apathetic patient may obtain sufficient energy to harm himself before his depression has been fully alleviated. ■ Niamid may potentiate sedatives, narcotics, hypnotics, analgesics, muscle relaxants, sympathomimetic agents, thiazide compounds and stimulants, including alcohol. Caution should be exercised when rauwolfia compounds and Niamid are administered simultaneously. Rare instances have been reported of reactions (including atropine-like effects, and muscular rigidity) occurring when imipramine was administered during or shortly after treatment with certain other drugs that inhibit monoamine oxidase. **In Cardiology:** The central effects of Niamid may encourage hyperactivity and the patient should be closely observed for any such manifestation. Orthostatic hypotension or hypertensive episodes occur in a few individuals; cardiac patients should be carefully selected and closely supervised. **In Epilepsy:** Although in some patients therapeutic benefits have been achieved with Niamid, in others the disease has been aggravated. Care should be exercised in the concomitant use of imipramine, since such treatment with monoamine oxidase inhibitors has been reported to aggravate the grand mal seizures. **In Tuberculosis:** Existing data do not indicate whether resistance of M. tuberculosis to isoniazid may be induced with Niamid therapy; nevertheless, it should be withheld in the depressed patient with coexisting tuberculosis who may need isoniazid. ■ As with all therapeutic agents excreted in part via the kidney, due caution in adjusting dosage in patients with impaired renal function should be observed. **Supplied:** Niamid (Nialamide) Tablets, 25 mg.: 100's—pink, scored tablets; 100 mg.: 100's—orange, scored tablets. *More detailed professional information available on request.*



hastens healing of most dermatoses

In most of the common dermatoses, infection, inflammation and allergy...either singly or in combination...play a critical etiologic role. By virtue of its dual components Sterosan-hydrocortisone effectively combats all three factors. As a result, Sterosan-hydrocortisone in clinical use effectively brings about healing in 80-90% of dermatoses[1-4]...is often effective in cases of long duration resistant to other topical therapy.[2-4] Available in both cream and ointment form, Sterosan-hydrocortisone is light in color...cosmetically acceptable for use on exposed areas.

References: (1) Lubowe, I. I.: Antibiot. Med. & Clin. Therap. **4**:81, 1957. (2) Fox, H. H.: Antibiot. Med. **6**:85, 1959. (3) Murphy, J. C.: Rocky Mountain M. J. **55**:53, 1958. (4) Pace, B. F.: Med. Rec. & Ann. **51**:370, 1957.

Sterosan®-hydrocortisone, brand of chlorquinaldol with hydrocortisone, Cream and Ointment containing 3% of Sterosan and 1% of hydrocortisone. Tubes of 5 and 20 Gm.

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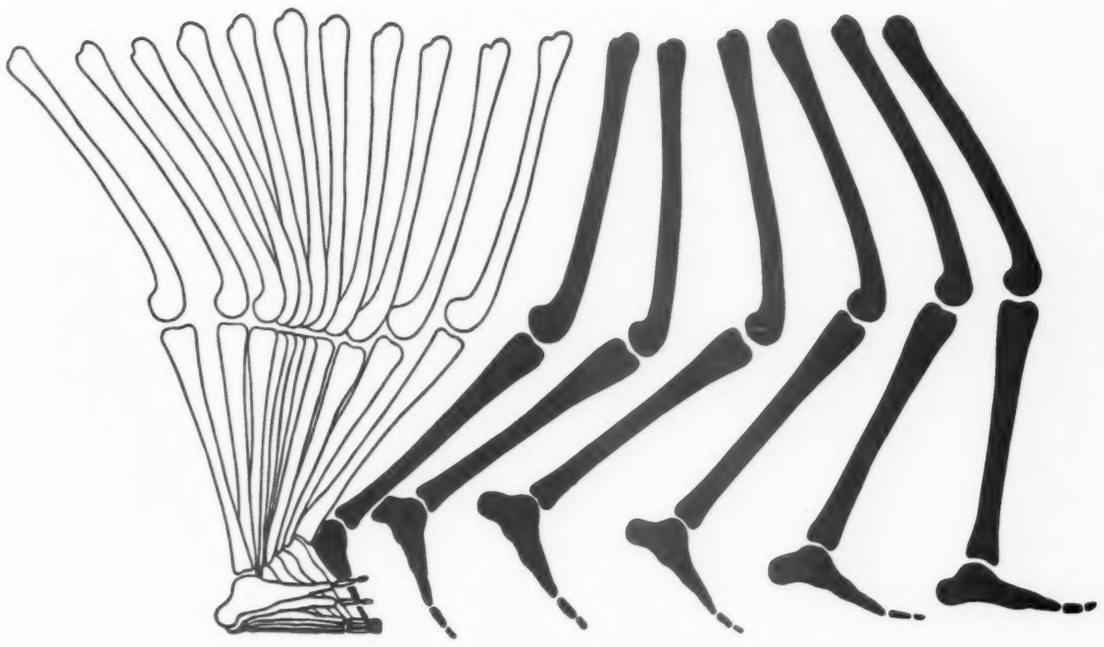

Depo-Medrol was administered intra-articularly to 118 patients (250 injections) for disorders including rheumatoid arthritis, osteoarthritis, epicondylitis, and tendinitis.

Relief of pain and swelling was marked or complete in 104 of the 118 (88.1%); duration of response to a single injection was more than three weeks in 89 patients (75.4%) and more than six weeks in 39 of these.[1] "Post-injection flare-up was practically non-existent."[1]

relief within hours... lasting for weeks

Depo-Medrol* intra-articularly

Indications and dosages

Intra-articular, intrabursal and intratendinous injections of Depo-Medrol are useful for sustained anti-inflammatory effect and symptomatic relief in rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, epicondylitis and other rheumatic disorders.

Intra-articular dosage depends on the size of the joint and the severity of the condition. Injections may be repeated, if necessary, at intervals of one to five weeks. A suggested dosage guide: Large joint, 20 to 80 mg.; medium joint, 10 to 40 mg.; small joint, 4 to 10 mg.

For administration directly into bursae, dosage may be 4 to 30 mg. (repeat injections are usually not needed).

For injection into the tendon sheath, 4 to 30 mg. is a usual range (in recurrent or chronic conditions, repeat injections may be needed).

Precautions

Depo-Medrol for local effect is contraindicated in the presence of acute infectious conditions. Infrequently, atrophic changes in the dermis may form shallow depressions in the skin at the injection site, but these usually disappear in a few months.

Depo-Medrol 40 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	40 mg.
Polyethylene glycol 4000	29 mg.
Sodium chloride	8.7 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 1 cc. and 5 cc. vials

20 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	20 mg.
Polyethylene glycol 4000	29.6 mg.
Sodium chloride	8.9 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 5 cc. vials

1. Norcross, B. M., and Winter, J. A.: Methylprednisolone acetate: a single preparation suitable for both intra-articular and systemic use, New York J. Med. *61*:552 (Feb. 15) 1961.

*Trademark, Reg. U. S. Pat. Off. methylprednisolone acetate, Upjohn

The Upjohn Company, Kalamazoo, Michigan

Upjohn

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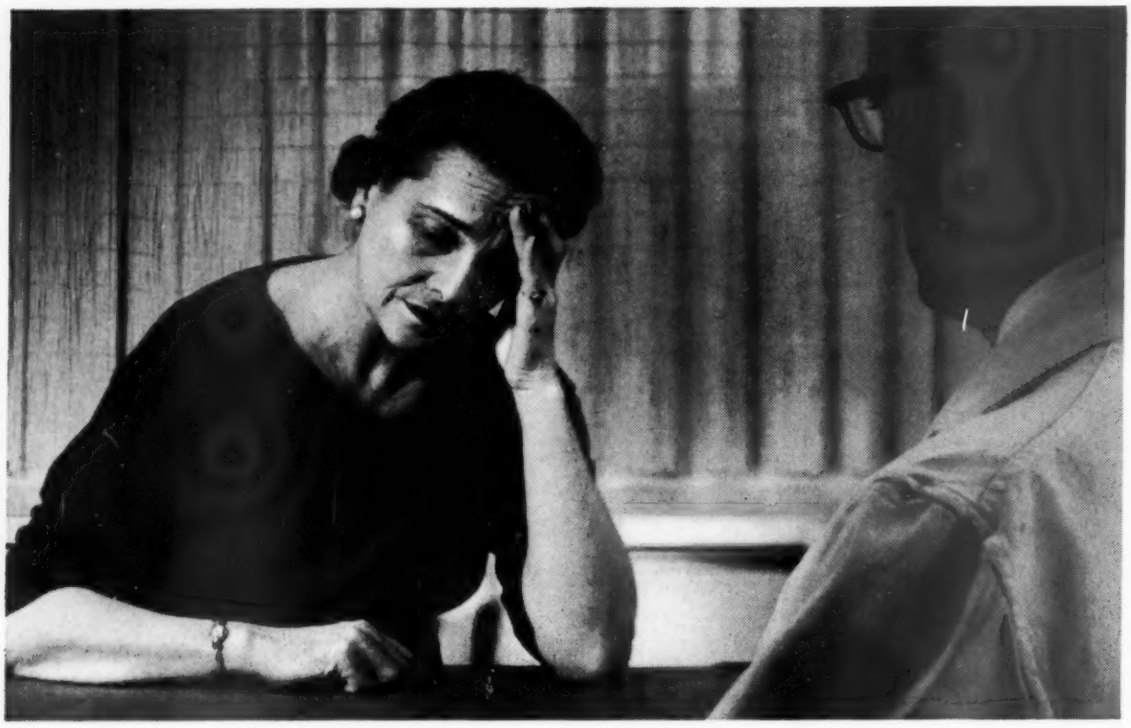
Helps you take the misery out of menopause

as hormones alone often don't do



Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

Dosage: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

Composition: Miltown (meprobamate) + conjugated estrogens (equine).

Supplied: **Milprem-400**, each coated pink tablet contains 400 mg. Miltown and 0.4 mg. conjugated estrogens (equine). **Milprem-200**, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Both potencies in bottles of 60.

Literature and samples on request.

Milprem®

(Miltown® plus natural estrogens)

CMP-1309

Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

This is where Milprem helps you so much. It calms the woman's anxiety and tension; prevents moody ups and downs; relieves her insomnia and headache. At the same time, it checks hot flushes by replacing lost estrogens. The patient feels better than she did on estrogen therapy alone. And your counsel and your assurances can now help her make her adjustment much faster.

WALLACE LABORATORIES/*Cranbury, N. J.*

aspirin buffered with the most widely-prescribed antacid...

in long-term administration, as in Arthritis,
when aspirin combined with an antacid is desired:

Specify **Ascriptin**® RORER

the aspirin buffered with the best

To prevent or minimize gastric distress which often accompanies prolonged or high level administration of acetylsalicylic acid, ASCRIPTIN provides aspirin in combination with MAALOX®, the preferred professional antacid. The recognized superiority of MAALOX makes ASCRIPTIN a superior aspirin-antacid, with the virtues of buffered aspirin and with the added distinction of being promoted professionally only.

Indicated wherever salicylates are useful, ASCRIPTIN is particularly suited to the long-term requirements of your arthritic patients.

Supplied: **Bottles of 100 and 500 tablets. For severe pain — Capsules ASCRIPTIN with Codeine (codeine phosphate 15 mg.), bottles of 50.**

RORER | WILLIAM H. RORER, INC. PHILADELPHIA, PENNSYLVANIA

Notable Success with VISTARIL...

in prepartum tension and anxiety		allays anxiety without impairing ability to cooperate during labor and delivery[1]	reduces narcotic requirements and incidence of narcotic-induced respiratory depression, helps control emesis[1,4]
in the cardiac or the hypertensive patient		allays anxiety without adverse influence on blood pressure[2]	helps correct certain functional arrhythmias, does not increase gastric secretion[2]
in problem drinkers		allays anxiety—makes patient more manageable[3]	produces no significant depression of blood pressure, pulse rate, or respiration. No liver involvement reported
in preoperative tension and anxiety		allays anxiety without depression of vital functions[4]	reduces incidence of narcotic-induced respiratory depression and hypotension, relaxes skeletal muscle, smooths recovery and helps control emesis[4]
in pediatrics		allays tension in agitated, hyperkinetic patients	avoids danger of liver damage or other untoward reactions

References: 1. Benson, C., and Benson, R. C.: Scientific Exhibit, Illinois Acad Gen Practice, Sept., 1960. **2.** Salmons, J. A.: Dis. Chest 38:105, 1960 **3.** Major, R. A.: GP 21:104, 1960. **4.** Grady, R. W., and Rich, A. L.: Scientific Exhibit, Am Soc. Anesth., New York, Oct. 4-7, 1960.

for successful
tranquilization—

Vistaril

ORAL/HYDROXYZINE PAMOATE
PARENTERAL/HYDROXYZINE HYDROCHLORIDE

effectively allays anxiety

no reported incidence of liver damage, respiratory depression or addiction

exerts helpful antiemetic, antisecretory, antipruritic effects

Science for the world's well-being®

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

IN BRIEF

Vistaril is hydroxyzine pamoate. The hydrochloride salt of hydroxyzine is used in the parenteral solution.

Vistaril acts rapidly in the symptomatic treatment of a variety of neuroses and other emotional disturbances manifested by anxiety, apprehension or fear—whether occurring alone or complicating a physical illness. Used preoperatively and prepartum, Vistaril controls anxiety and fear, permits a substantial reduction in the amount of meperidine or other narcotic required for satisfactory analgesia, and helps prevent emesis. Vistaril's calming effect usually does not impair discrimination, and is accompanied by direct and secondary muscle relaxation. No toxicity has been reported with Vistaril, and it has a remarkable record of freedom from reactions.

INDICATIONS: Vistaril is clinically effective in anxiety and tension states, senility, anxiety associated with various disease states, alcoholism, pre- and postpartum and pre- and postoperative tension and emesis, certain functional arrhythmias, and pediatric behavior problems.

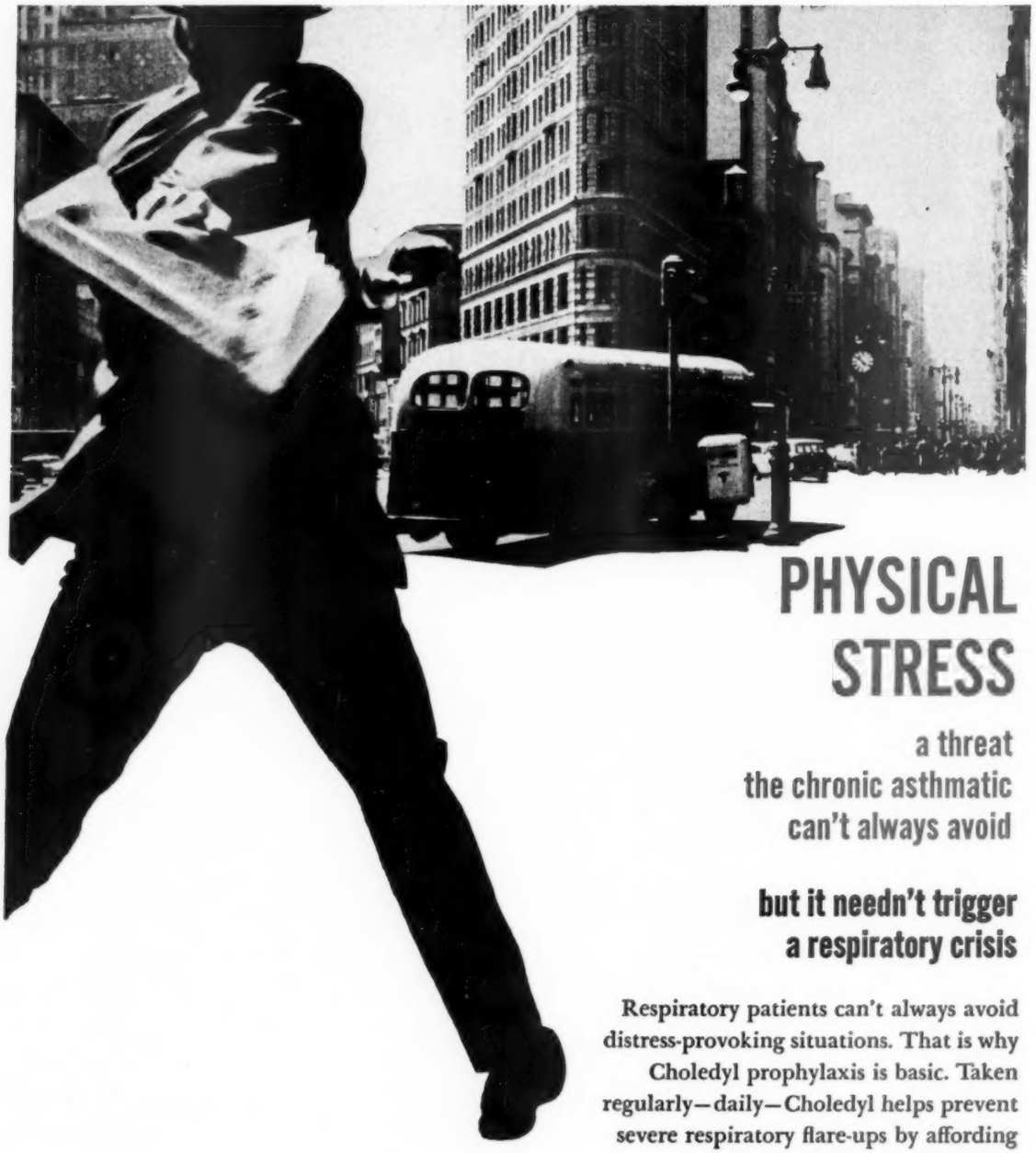
ADMINISTRATION AND DOSAGE: Dosage varies with the state and response of each patient, rather than with weight and should be individualized by the physician for optimum results. *Recommended oral dosage:* In anxiety and tension states, senility, alcoholism, pre- and postoperative and pre- and postpartum tension and emesis: up to 400 mg. daily in divided doses. In anxiety associated with asthma, neurodermatoses, menopausal syndrome, digestive disorders, functional or essential hypertension, tension headaches: 50 mg. q.i.d. initially—adjust according to response. In cardiac arrhythmias: initial—25 mg. q. 6 h. until arrhythmia disappears; maintenance or prophylactic—50-75 mg. daily in divided doses. In pediatric behavior problems under 6 years: 50 mg. daily in divided doses. Six and over: 50-100 mg. daily in divided doses. *Recommended parenteral dosage:* In preoperative, obstetrical, and more emergent situations in other indications: 25-100 mg. I.M. or I.V. q. 4 h., p.r.n. In cardiac arrhythmias: 50-100 mg. I.M. stat, and q. 4-6 h., p.r.n.; maintain with 25 mg. b.i.d. or t.i.d.

SIDE EFFECTS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Dryness of mouth may be encountered at higher doses.

PRECAUTIONS: The potentiating action of hydroxyzine should be taken into account when the drug is used in conjunction with central nervous system depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is usually for 24-48 hours, except when, in the judgement of the physician, longer-term therapy by this route is desirable.

SUPPLIED: VISTARIL *Capsules* (hydroxyzine pamoate)—25, 50, and 100 mg. VISTARIL *Oral Suspension* (hydroxyzine pamoate)—25 mg. per 5 cc. teaspoonful. VISTARIL *Parenteral Solution* (hydroxyzine hydrochloride)—10 cc. vials, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc.

More detailed professional information available on request.



PHYSICAL STRESS

a threat the chronic asthmatic can't always avoid

but it needn't trigger a respiratory crisis

Respiratory patients can't always avoid distress-provoking situations. That is why Choledyl prophylaxis is basic. Taken regularly—daily—Choledyl helps prevent severe respiratory flare-ups by affording sustained bronchodilatation. Throughout long-term use, Choledyl is uniformly effective. And even in older patients, gastric upset and other unwanted effects are rare.
Dosage: one 200 mg. tablet q.i.d.

Precautions: Side effects have been minimal but may include CNS stimulation or, rarely, palpitation. Full dosage information, available on request, should be consulted before initiating therapy.

to avoid the crisis in chronic bronchitis, chronic asthma, emphysema

CHOLEDYL®

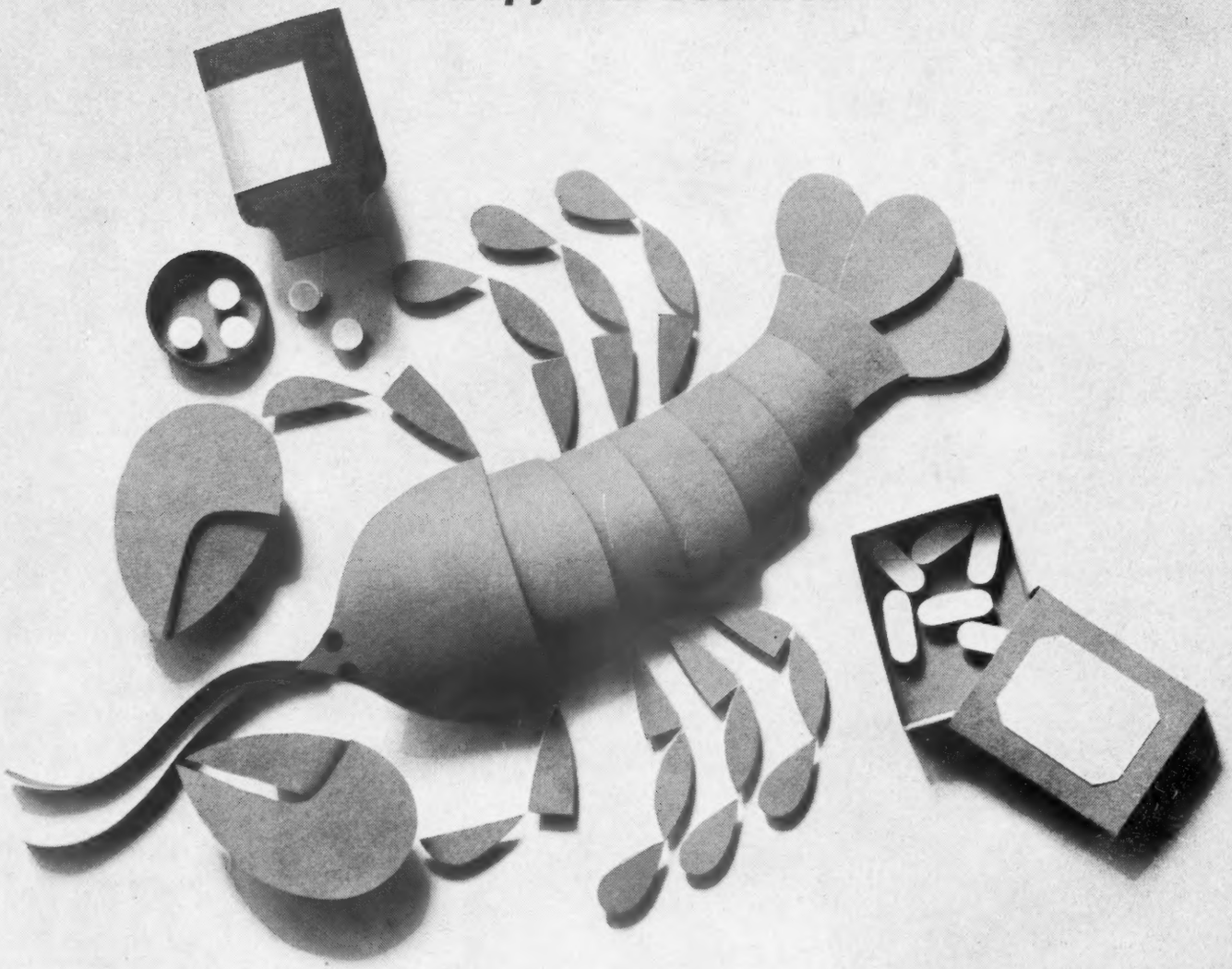
brand of oxtriphylline

6P14

THE CHOLINE SALT OF THEOPHYLLINE

WARNER CHILCOTT
MORRIS PLAINS, N.J.

in severe drug and food sensitivity... rapid relief and control of symptoms on short-term therapy with Decadron®



Brief treatment with DECADRON – orally or parenterally – can provide rapid and effective control of allergic emergencies and acute allergic disorders such as reactions to foods, drugs, plants, weeds, and animals. In 40 patients given Injection DECADRON Phosphate, "subjective improvement was often noticed within one hour and objective improvement recorded within 4 hours."[1] Therapeutic doses of steroids may help prevent recurrences of severe allergic states, without interfering with desensitization or other immunity procedures.[2]

Before prescribing or administering DECADRON, the physician should consult the detailed information on use accompanying the package or available on request.

References: 1. Grater, W. C.: Southern M. J. 53:1144, 1960. 2. Feinberg, S. M.: Med. Sci. 6:(No. 3) 181, 1959.

Supplied: As 0.75 mg. and 0.5 mg. scored, pentagon-shaped tablets in bottles of 100 and 1000. As Injection DECADRON Phosphate in 5 cc. vials, each cc. containing 4 mg. of dexamethasone 21-phosphate as the disodium salt; inactive ingredients: 8 mg. creatinine, 10 mg. sodium citrate; sodium hydroxide to pH 7.8, and water for injection q. s. 1 cc.; preservatives: 0.32 per cent sodium bisulfite and 0.5 per cent phenol. DECADRON is a trademark of Merck & Co., Inc.

MERCK SHARP & DOHME Division of Merck & Co., INC., West Point, Pa.

Decadron®

Dexamethasone

TREATS MORE PATIENTS MORE EFFECTIVELY

DECADRON: Recommended dosage schedule in the treatment of drug and food sensitivity reactions

time	amount	administration
1st day	one to two cc. (4 to 8 mg.) Injection DECADRON Phosphate intramuscular	repeated as necessary (In substituting tablet therapy, give the first oral dose four or five hours before the final parenteral dose.)
2nd day	two 0.75 mg. Tablets DECADRON	b.i.d.
3rd day	two 0.75 mg. Tablets DECADRON	b.i.d.
4th day	one 0.75 mg. Tablet DECADRON	b.i.d.
5th day	one 0.75 mg. Tablet DECADRON	per day
6th day	one 0.75 mg. Tablet DECADRON	per day
7th day	RETURN VISIT	

vertigo is reversible

Antivert stops vertigo

moderate to complete relief of symptoms in 9 out of 10 patients[1]

Prescribe one ANTIVERT tablet (or 1-2 teaspoonfuls ANTIVERT syrup) 3 times daily, before each meal, for prompt relief of vertigo, Meniere's syndrome and allied disorders. Side effects are short-lived, usually only harmless flushing and tingling associated with vasodilation. As with all vasodilators, ANTIVERT is contraindicated in severe hypotension and hemorrhage.

Supplied: Small blue-and-white scored tablets (meclizine HCl 12.5 mg. and nicotinic acid 50 mg.) in bottles of 100. Syrup (each 5 cc. teaspoonful contains meclizine HCl 6.25 mg. and nicotinic acid 25 mg.) in pint bottles. Prescription only. Bibliography available on request.

Reference: 1. Scal, J. C.: Eye Ear Nose & Throat Month. **38**:738 (Sept.) 1959.

And for your aging patients—
NEOBON® Capsules
five-factor geriatric supplement

ROERIG

New York 17, N.Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being®

Quietude for the Hypertensive

As relaxing as a mountain lake...

BUTISERPINE® separates the hypertensive from his anxieties and tensions, lowering the blood pressure conservatively but effectively.

With its gentle calming and hypotensive actions, Butiserpine does not set up a chain of side effects. Its *low* reserpine content (0.1 mg. per tablet) reduces blood pressure smoothly; its 15 mg. of noncumulative BUTISOL SODIUM® butabarbital sodium induces relaxation without depression.

Available as: Butiserpine Tablets, Elixir, Prestabs® Butiserpine R-A
(Repeat Action Tablets)

McNEIL McNEIL LABORATORIES, INC., Fort Washington, Pa.

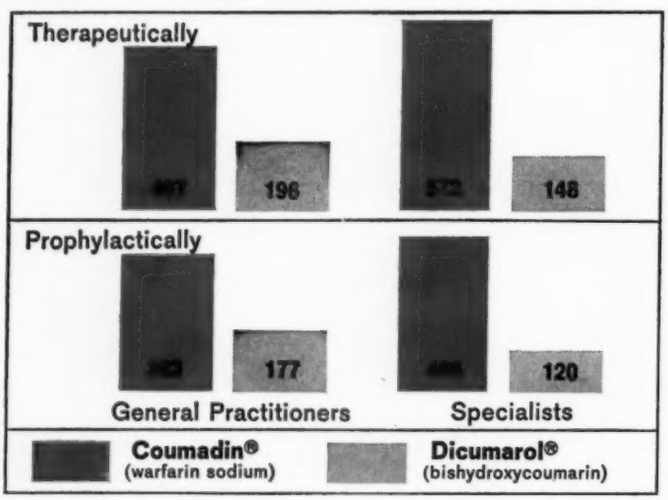
No. 2 of a series reporting on Endo Laboratories' Anticoagulant Survey

Nationwide Survey Explores Current Use of Anticoagulants in Angina Pectoris

In the first of this series of reports on the current application of oral anticoagulants in daily practice, data based on replies from 10,016 physicians showed that these agents were being widely used in *long-term therapy of myocardial infarction.*

Since the anginal syndrome may be the herald of coronary thrombosis and myocardial infarction, it is of interest to note whether anticoagulants are being employed therapeutically and prophylactically in patients with angina.

The following graph, based on Endo Laboratories' *Anticoagulant Survey*, demonstrates the extent to which anticoagulation is used in *angina pectoris* among 3,092 general practitioners and 2,626 specialists prescribing Coumadin® most often, as compared to 1,689 general practitioners and 804 specialists using Dicumarol.®



Physicians Treating Angina Pectoris with Oral Anticoagulants—Therapeutically and Prophylactically

While the use of anticoagulants in angina pectoris was higher among specialists than among general practitioners, both used Coumadin® more frequently than Dicumarol.® Tabulation[1] of all replies to *Anticoagulant Survey* has shown that 61.4 per cent of responding physicians prescribed Coumadin® most often, as compared to 27.6 per cent who prescribed Dicumarol,® the *second* most frequently specified oral anticoagulant—a ratio of more than 2:1.

Anticoagulants Widely Used in Coronary Artery Disease

Because of the relationship of the anginal syndrome to *coronary atherosclerosis, coronary insufficiency,* and *impending myocardial infarction,* it is also interesting to note the percentage of physicians who reported their use of anticoagulants in *these* conditions.[1]

Indication	All Anticoagulants	
	Therapeutically	Prophylactically
Coronary Atherosclerosis	11.3%	10.2%
Coronary Insufficiency	29.2%	23.8%
Impending Myocardial Infarction	52.5%	39.9%

Percentage of Physicians Using Anticoagulants in Other Coronary Artery Disease

Anticoagulant Therapy May Prevent First Myocardial Infarction

The findings of *Anticoagulant Survey* are consonant with recently reported clinical experience demonstrating the value of long-term anticoagulation in angina pectoris. For example, on the basis of his results in general office practice, Nora[2] believes that "*long-term anticoagulation therapy not only reduces the probability of myocardial infarction in patients having sustained previous infarctions but is effective in preventing a first infarction in patients with angina.*" The drug used by Nora was Coumadin.

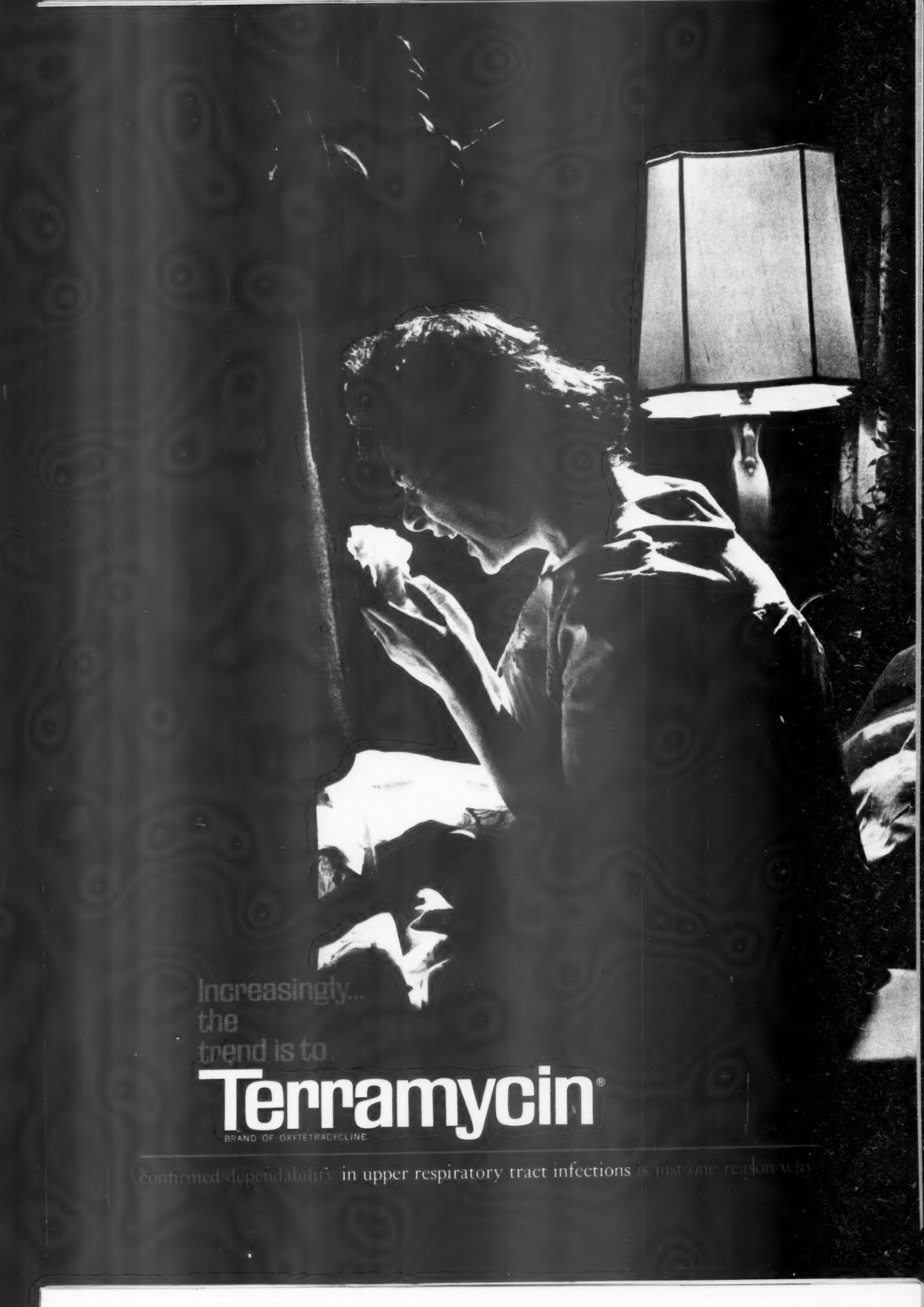
"The most significant advantage is the great ease in maintaining patients in a therapeutic range. It has been rewarding to find, month after month, patients varying no more than three or four seconds in their prothrombin times on their established dosage of [Coumadin]."[2]

1. Littman, M. L.; Barrett, E. A., and Shapiro, S.: Scientific Exhibit, 110th Annual Meet., A.M.A., New York, N. Y., June 25-30, 1961. 2. Nora, J. J.: M. Times 89:502, May, 1961; idem: J.A.M.A. 174:118, Sept. 10, 1960.

Another professional service of Endo Laboratories—makers of
COUMADIN®
the proven anticoagulant
for long-term maintenance
FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE

Coumadin (warfarin sodium) is manufactured under license from the Wisconsin Alumni Research Foundation, and is supplied as scored tablets of 2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; and 25 mg., red, as well as in 50 mg. and 75 mg. single-injection units.

Endo®
ENDO LABORATORIES • Richmond Hill 18, New York


Increasingly...
the
trend is to
Terramycin®
BRAND OF OXYTETRACYCLINE
confirmed dependability in upper respiratory tract infections is just one reason why

Jacques and Fuchs* recently reported on experience with Terramycin in 106 patients with a variety of acute and chronic upper respiratory tract infections, many of which had failed to respond to other antibiotics. Oral dosage was preceded by intramuscular injection in 44 cases. "It was the impression of the hospital staff that oxytetracycline [Terramycin] was not only better tolerated, but more effective than other antibiotics habitually used."

The investigators noted that "some of the best results were seen in patients who were most severely ill."

According to the authors, the availability of Terramycin as a preconstituted intramuscular solution makes it feasible "to treat serious infections with a broad-spectrum antibiotic that has rapid action, and to continue with the same antibiotic given orally as soon as the infection is brought under control."

The results reported in this and many other studies confirm the vitality of Terramycin for broad-spectrum antibiotic therapy and demonstrate why—increasingly—the trend is to Terramycin.

In brief

The dependability of Terramycin in daily practice is based on its broad range of antimicrobial effectiveness, excellent toleration, and low order of toxicity. As with other broad-spectrum antibiotics, overgrowth of nonsusceptible organisms may develop. If this occurs, discontinue the medication and institute appropriate specific therapy as indicated by susceptibility testing. Glossitis and allergic reactions to Terramycin are rare. As with all I.M. preparations, injection should be made within the body of a relatively large muscle. Care should always be taken to avoid injection into a major nerve or its surrounding sheath. For complete dosage, administration, and precaution information, read package insert before using.

More detailed professional information available on request.

Terramycin®

BRAND OF OXYTETRACYCLINE

INTRAMUSCULAR SOLUTION

50 mg./cc. in 10 cc. vials; 100 mg. and 250 mg. in 2 cc. ampules

the broad-spectrum antibiotic ready for immediate intramuscular injection . . . conveniently preconstituted . . . notably well tolerated at injection site with low tissue reaction compared to other broad-spectrum antibiotics

another reason why the trend is to Terramycin—*versatility of dosage form:*

TERRAMYCIN Capsules
250 mg. and 125 mg. per capsule—for convenient initial or maintenance therapy in adults and older children

TERRAMYCIN Syrup / Pediatric Drops
125 mg. per tsp. and 5 mg. per drop (100 mg./cc.), respectively—deliciously fruit-flavored, preconstituted aqueous suspensions

Science for the world's well-being® Pfizer

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc.
New York 17, N. Y.

*Jacques, A. A., and Fuchs, V. H.: J. Louisiana M. Soc 113:200, May, 1961.

Pfizer *Science for the world's well-being®*

Dear Doctor:

Reports from our representatives indicate that many physicians would appreciate simplification for prescription-writing purposes of the names of Terramycin products in both the "plain" and the "Cosa" dosage forms.

The "Cosa" forms originated, you may recall, on the basis of clinical evidence of enhanced antibiotic absorption when glucosamine is employed in oral administration. To permit each physician individually to study this evidence and choose which form he would prefer to prescribe, we offered Terramycin in both forms—that is, in the regular Terramycin forms without glucosamine, and in the "Cosa" forms with glucosamine.

This distinction appears to be no longer necessary since glucosamine, a highly acceptable excipient for oral antibiotics, now is being incorporated uniformly in all such forms, thereby simplifying nomenclature and your prescription writing.

Accordingly, and effective immediately, forms incorporating glucosamine will be offered simply as Terramycin without the "Cosa" prefix.

To make clear just which forms are affected, please refer to the brief tabulation (below) of Terramycin dosage forms both *before* and *after* this change. We are also requesting our representative to call on you at an early date to answer any questions that may arise.

We feel certain that this action, prompted by your comments and those of many other physicians, will simplify your writing of prescriptions for Terramycin products.

We welcome your comments on this action and on any other phase of our operations, since it is our objective to render every service as efficiently as possible to our friends in the medical profession.

Sincerely,
PFIZER LABORATORIES

The following table indicates the former name and the current name of Terramycin systemic preparations:

FORMERLY NAMED	NOW NAMED
Cosa-Terramycin® Capsules	**Terramycin**® Capsules*
Cosa-Terrabon® Oral Suspension	**Terramycin** Syrup
Cosa-Terrabon Pediatric Drops	**Terramycin** Pediatric Drops

and simpler names for these Terramycin-containing formulations:

Cosa-Terrastatin® Capsules	**Terrastatin**® Capsules
Cosa-Terrastatin for Oral Suspension	**Terrastatin** for Oral Suspension
Cosa-Terracydin® Capsules	**Terracydin**® Capsules

. . . and these names remain unchanged:

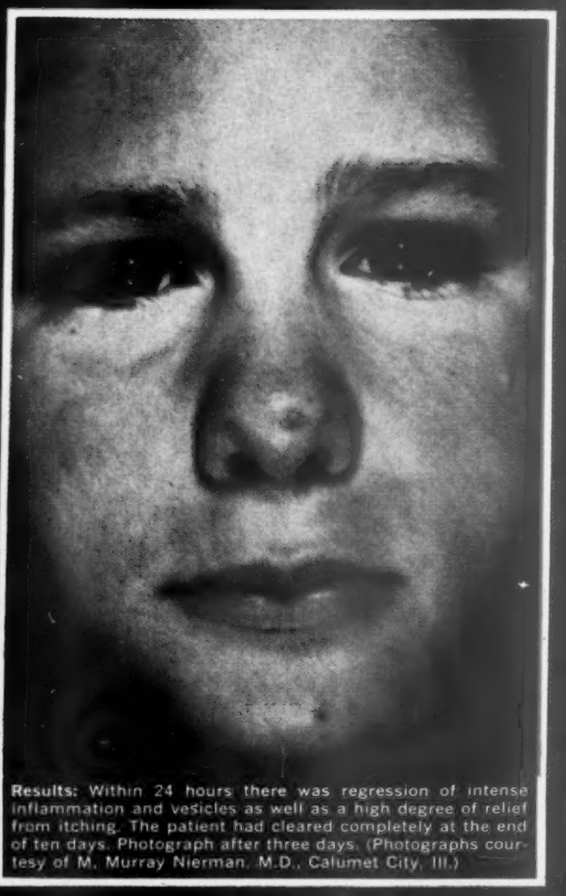
Terramycin Intramuscular Solution
Terramycin Intravenous

**Terramycin Capsules* without glucosamine *are no longer available.*

The clinical versatility of Terramycin is enhanced by its specialized dosage forms adapted to individual needs—*another reason for the trend to Terramycin.*

Male, Age 9; Dx: Poison Ivy Dermatitis.
Rx: Celestone, 1 tab. q.i.d. for two days, 1 tab. t.i.d. for two days, 1 tab. b.i.d. for one week, and 1 tab. daily for 7 days. Photograph shows the patient before treatment.

Allergic/inflammatory flare-up!



Results: Within 24 hours there was regression of intense inflammation and vesicles as well as a high degree of relief from itching. The patient had cleared completely at the end of ten days. Photograph after three days. (Photographs courtesy of M. Murray Nierman, M.D., Calumet City, Ill.)

Schering

A new achievement in corticosteroid activity: CELESTONE (betamethasone) has been called "perhaps the most important step ahead since the discovery of prednisone and prednisolone..."[1] and "unquestionably the most active adrenocortical steroid we have studied to date."[2] Pre-introductory clinical studies have established not only the high antiallergic/anti-inflammatory activity of CELESTONE but also its "low incidence of side effects... [and] absence of new toxic effects...."[3]

Three significant clinical advantages: In reporting results of a study of 154 dermatologic patients, treated up to 9 months, the investigators[1] cite as "three important clinical advantages of betamethasone [CELESTONE]: its almost uniform effectiveness at exceptionally low dosages, the striking absence of hormonal side effects in our series, and the ability of this corticosteroid to elicit a good therapeutic response in patients who had previously done poorly on other steroids."

Rapid remission with new Celestone

the first major advance in corticosteroid therapy in over 2½ years

Greater utility–ease of use: Gratifying results have been achieved with CELESTONE in a broad range of steroid-responsive disorders, from bronchial asthma and pollenosis to allergic dermatoses, inflammatory ocular diseases and rheumatoid arthritis. Rapid subsidence of allergic or inflammatory flare-up can usually be expected on average daily dosages of from 2 to 8 tablets. The single tablet strength (0.6 mg.) simplifies dosage schedules and facilitates proper dosage adjustment when patients are switched from other corticosteroids. H-390

Safety-speed factor: Results with CELESTONE in 353 dermatologic patients[2] indicate that "its high degree of effectiveness and virtual absence of side effects in low dosages, which permit a simplified therapeutic regimen, make betamethasone [CELESTONE] an exceptionally useful corticosteroid in acute, short-term conditions."

For complete details, consult latest Schering literature available from your Schering Representative or the Medical Services Department, Schering Corporation, Bloomfield, New Jersey.

Bibliography: 1. Gant, J.Q., and Gould, A.H.: Betamethasone: A Clinical Study. Paper presented at First Conference on the Clinical Application of Betamethasone – A New Corticosteroid, New York City, May 8, 1961. 2. Nierman, M.M.: The Use of Betamethasone in Dermatology. *Ibid.* 3. Frank, L.: The Place of Betamethasone in Dermatologic Practice. *Ibid.*

NEW CELESTONE™

(betamethasone) **Tablets 0.6 mg.**

Excerpts from a 2-year study of 87 patients

USE OF DEPROL IN THE OFFICE TREATMENT OF DEPRESSION*

"Eighty-seven patients were studied during a period of over 2 years. All were psychoneurotic, and all were seen in private psychiatric practice. Although diagnoses differed, the most prominent symptom in each case was severe depression... Patients ranged in age from 16 to 70 years; the greater portion were 20 to 40 years old.

"The usual starting dosage of Deprol† was 1 tablet 4 times a day... If necessary, this dosage was increased to 6 tablets per day, and then to 8."

Results

"All except 2 of the 87 patients treated with Deprol were definitely helped by this medication.

"Deprol was found most useful in patients with pronounced depressions characterized by apathy, withdrawal, and inability to perform. Such patients were relieved of their oppressive despondency and crying spells and became accessible to psychotherapy. They became more hopeful and more willing and able to expend effort to help themselves. They were able to sleep well, to enjoy their food again, to concentrate better, to make decisions and to return to normal activity...

"Unlike most other drugs used for depression, [Deprol] is also effective in controlling a wide spectrum of associated symptoms, particularly anxiety, tension, sleep disturbances, and psychosomatic complaints. Deprol does not depress appetite but permits its normal return as the patient improves. It is not a euphoriant; rather, patients taking the drug experience a return to a stable and normal mood."

Side Effects and Toxicity

During the two years of this study "...no side-effects were observed. Two patients who attempted suicide by ingesting, respectively, 40 and 30 tablets of Deprol experienced prolonged sleep with slight, transient fall in blood pressure, but they recovered without treatment and without sequelae."

Conclusion

"Deprol marks a definite step forward in the safe and effective treatment of depression."

*Ruchwarger, A.: M. Ann. District of Columbia *28*:438, Aug. 1959.
†Supplied by WALLACE LABORATORIES, Cranbury, N. J.

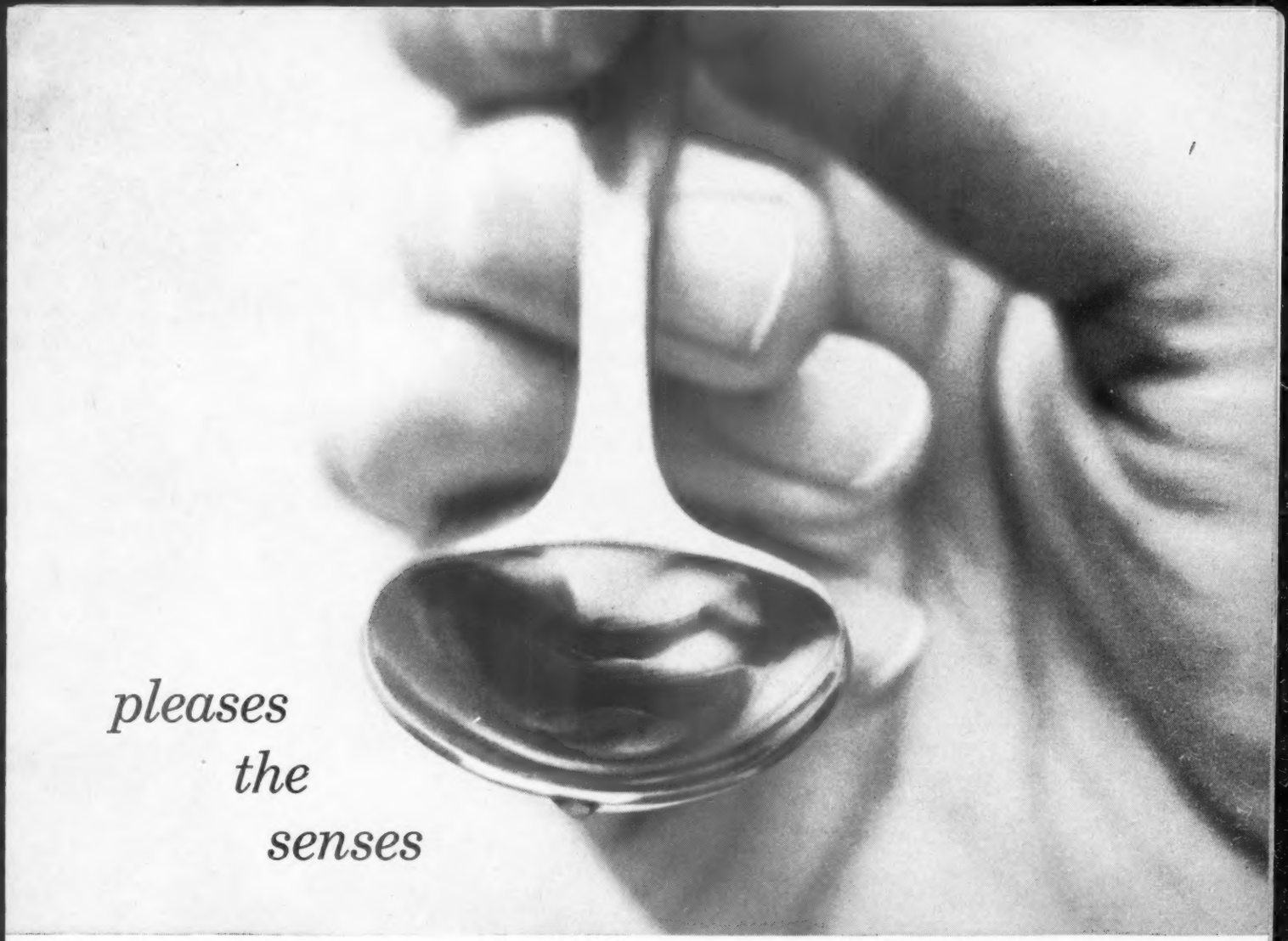
▲Deprol▲®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

Supplied: Bottles of 50 light-pink, scored tablets.

CD-5622



...as it eases the respiratory allergy

NORISODRINE® syrup

with calcium iodide

Whether he's afflicted with allergic sniffle or outright asthma, a cooperative patient can mean half the battle. That's why a treatment that's no chore to take can be so important. And that's what you get in Norisodrine Syrup.

You'll find, first, with Norisodrine Syrup a bronchodilator-expectorant useful in controlling a wide range of respiratory allergies. You'll *also* find that there's nothing easier on the senses than Norisodrine Syrup—golden color, fresh mint taste, pleasant smell.

Time and again, Norisodrine Syrup's value has been proved in patients with chronic cough, wheeze, or other classic asthma symptoms.

In a study[1] covering the treatment of 150 patients —ranging in age from one to seventy-three years— 133 reported good to excellent results.

Conclusions were: "Norisodrine Syrup diminished cough, brought about easy expectoration of mucus from the bronchial tree, lessened tightness in the chest, improved respiration."

Consider good-tasting Norisodrine Syrup for your next respiratory allergy patient. It can help you manage symptoms that have been troublesome for years.

[1]Frohman, I. P., A New Antitussive Agent, M. Times, 88:924, Aug. 1960.

Norisodrine: Isoproterenol Sulfate, Abbott.

ABBOTT

109241

extends the usefulness of Vitamin K_1 therapy†...

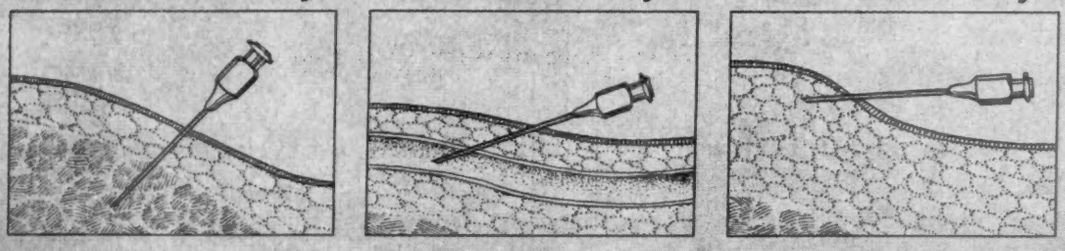
NEW Injection

Aqua

AQUEOUS COLLOIDAL SOLUTION

†a clear, stable, aqueous colloidal solution for administration

• intramuscularly • intravenously • subcutaneously



a dosage form for every Vitamin K indication:

AquaMEPHYTON (for intramuscular, intravenous, subcutaneous administration), 1-cc. ampuls containing 10 mg. MEPHYTON, Vitamin K_1

TABLETS MEPHYTON (for oral administration), 5 mg.

EMULSION MEPHYTON (for intravenous administration only), 1-cc. ampuls containing 10 mg. and 50 mg. per cc.

MEPHYTON®

OF MEPHYTON®, VITAMIN K_1

Vitamin K_1 "has a more prompt, more potent and more prolonged effect than the vitamin K analogues" *

*Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1960, p. 732

reduces the hazard of hemorrhage due to hypoprothrombinemia in:

- prophylaxis and therapy of hemorrhagic disease of the newborn
- surgery, preoperatively and postoperatively
- anticoagulant-induced prothrombin deficiency
- inadequate absorption of Vitamin K
- biliary tract disease
- prothrombin-depressing drugs such as salicylates and phenylbutazone
- inadequate endogenous production of Vitamin K

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

MSD **MERCK SHARP & DOHME**
DIVISION OF MERCK & CO., INC., WEST POINT, PA.

AquaMEPHYTON AND MEPHYTON ARE TRADEMARKS OF MERCK & CO., Inc.

Renese®

POLYTHIAZIDE

a more clinically useful diuretic/antihypertensive

IN BRIEF

RENESE (polythiazide) is a new, highly potent, orally effective, nonmercurial diuretic, saluretic, and antihypertensive agent with a high therapeutic index, low order of toxicity, and an intrinsically prolonged duration of action which enhances the excretion of sodium and chloride by the renal tubules.

INDICATIONS: RENESE is indicated for the treatment of hypertension and edema. It has been found useful in congestive heart failure, fluid retention of pregnancy, premenstrual tension, obesity (where fluid retention is present), renal edema, cirrhosis, drug-induced edema, and toxemia of pregnancy.

ADMINISTRATION AND DOSAGE: *Initial dose:* Depending on the severity of the conditions, initial doses of RENESE may range from 1 mg. to 4 mg. daily (refractory cases may require as much as 12 mg. daily). *Maintenance dose:* Usual effective maintenance doses range from 1 mg. to 4 mg. daily, depending on the severity of the cases. Some patients have responded to 1 mg. every other day (0.5 mg. daily).

SIDE EFFECTS AND PRECAUTIONS: Since all diuretic agents may reduce serum levels of sodium, chloride, and potassium, patients on RENESE should be observed regularly for early signs of fluid or electrolyte imbalance. Caution must be exercised during digitalis administration to prevent hypokalemia since patients are then more sensitive to the development of digitalis toxicity. During RENESE therapy of edema in patients with chronic renal disease, routine precautions should be taken against renal failure as indicated by an increasing blood urea nitrogen. Like other thiazide diuretics, RENESE may cause a rise in serum uric acid levels and should therefore be used with caution in patients with gout. Should overt manifestations of gout appear, the concomitant use of uricosuric agents may be effective in relieving the symptoms. Side effects with RENESE, such as nausea, vertigo, weakness, and fatigue are infrequent and seldom require cessation of therapy. Most of these reactions may be overcome by reducing the dose of RENESE or by taking measures to improve any electrolyte imbalance. Mild maculopapular skin rash has been rarely reported. Extra precautions may be necessary in patients who may require norepinephrine, or curare or its derivatives.

SUPPLIED: RENESE is available as 1 mg., white, scored tablets in bottles of 30; 2 mg., yellow, scored tablets in bottles of 30; 4 mg., white, scored tablets in bottles of 30.

More detailed professional information available on request.

new Renese®

POLYTHIAZIDE

1 mg. 2 mg. 4 mg.

A MORE CLINICALLY USEFUL
DIURETIC/ANTIHYPERTENSIVE

active antihypertensive
broad benefit
clinically confirmed
convenient control
dosage dexterity
dependable diuresis
enhanced effectiveness
foremost flexibility
increased individualization
long lasting
marked micturition
notable natruresis
orally optimal
peak potency
prolonged performance
reliable response
significant saluresis
tested toleration
unsurpassed utility
valuable versatility

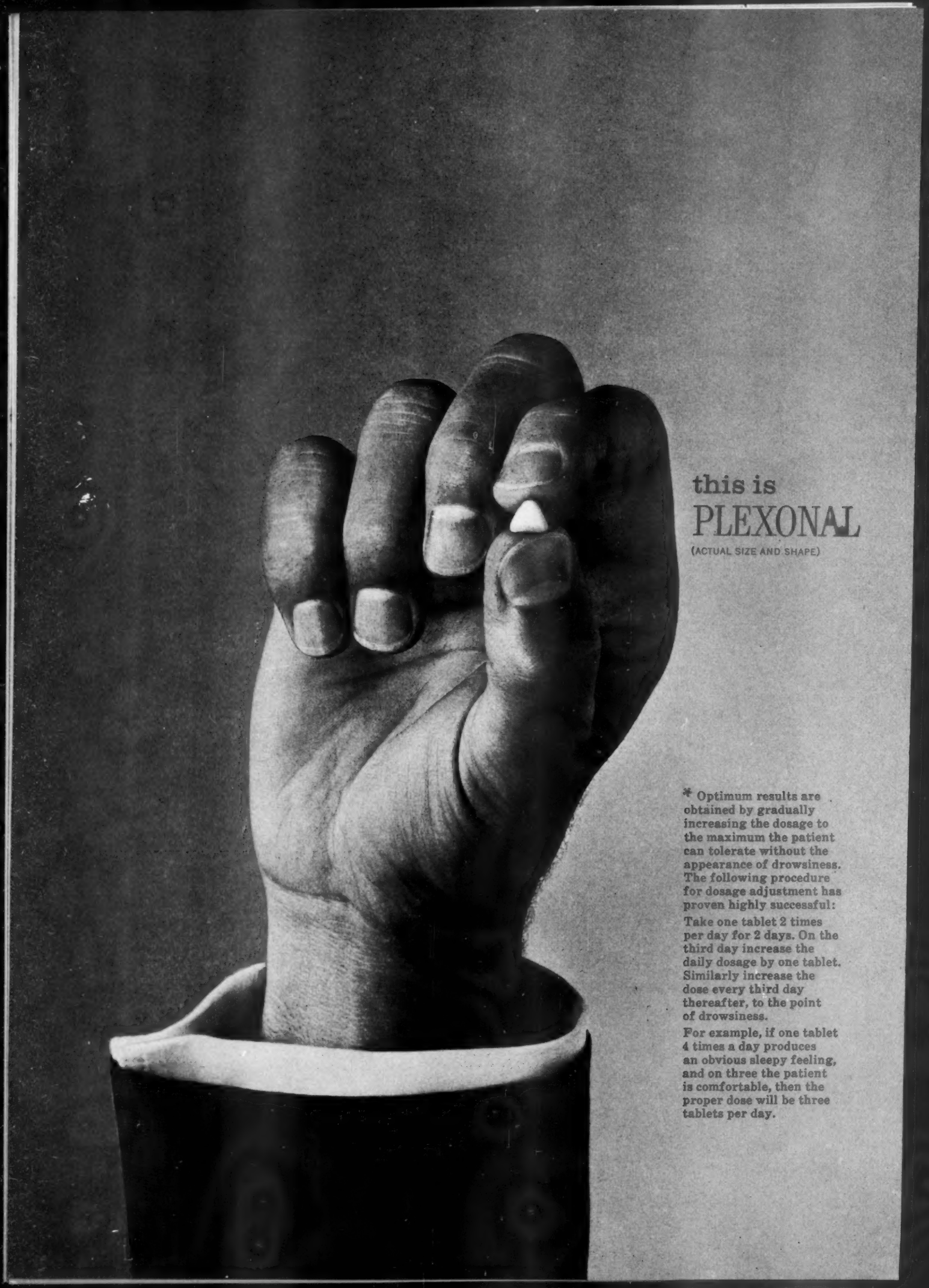
"enhanced effectiveness"

– In a 24-hour dose response study, RENESE produced a greater increase in sodium excretion than has been shown with four other currently available thiazides. In a controlled study[1] of patients with hypertensive cardiovascular disease, free of detectable edema, the 24-hour urinary volume increased by an average of 1.8 liters with an accompanying average weight reduction of 1.4 Kg. following a single 8 mg. dose of RENESE. The enhanced effectiveness of RENESE may produce response where previous therapy has failed or improve the response to present therapy.

1. Ford, R. V.: Current Therap. Res. 3:320, July, 1961

Pfizer *Science for the world's well-being®*

PFIZER LABORATORIES Division,
Chas. Pfizer & Co., Inc. New York 17, New York



* Optimum results are obtained by gradually increasing the dosage to the maximum the patient can tolerate without the appearance of drowsiness. The following procedure for dosage adjustment has proven highly successful:

Take one tablet 2 times per day for 2 days. On the third day increase the daily dosage by one tablet. Similarly increase the dose every third day thereafter, to the point of drowsiness.

For example, if one tablet 4 times a day produces an obvious sleepy feeling, and on three the patient is comfortable, then the proper dose will be three tablets per day.

a superior daytime relaxing agent

(NOT A TRANQUILIZER)

PLEXONAL®

Comparative clinical studies show that PLEXONAL is superior to meprobamate or barbiturates for daytime relaxation[1,2]

"Plexonal was preferred (superior therapeutic effect) by 73.7 per cent of the patients, whereas 11.1 per cent preferred meprobamate, a ratio of 6.6 to 1. . . . 30.5 per cent noted adverse reactions to meprobamate as compared to 7 per cent in respect to Plexonal. . . . Plexonal gave better results than did any of the sedative or relaxing agents that have been available during our experience covering the previous 15 years."[1]

In 26 older age cardiac patients, "A comparison of Plexonal with the therapy previously employed showed that 17 did better on Plexonal than on meprobamate, 6 did better on meprobamate than on Plexonal and 3 responded the same to both."[2]

Indications: Anxiety, tension, apprehension, nervousness, irritability, restlessness, hyperexcitability.

Extremely well tolerated by geriatric patients who need mild sedation, as well as by depressed patients.

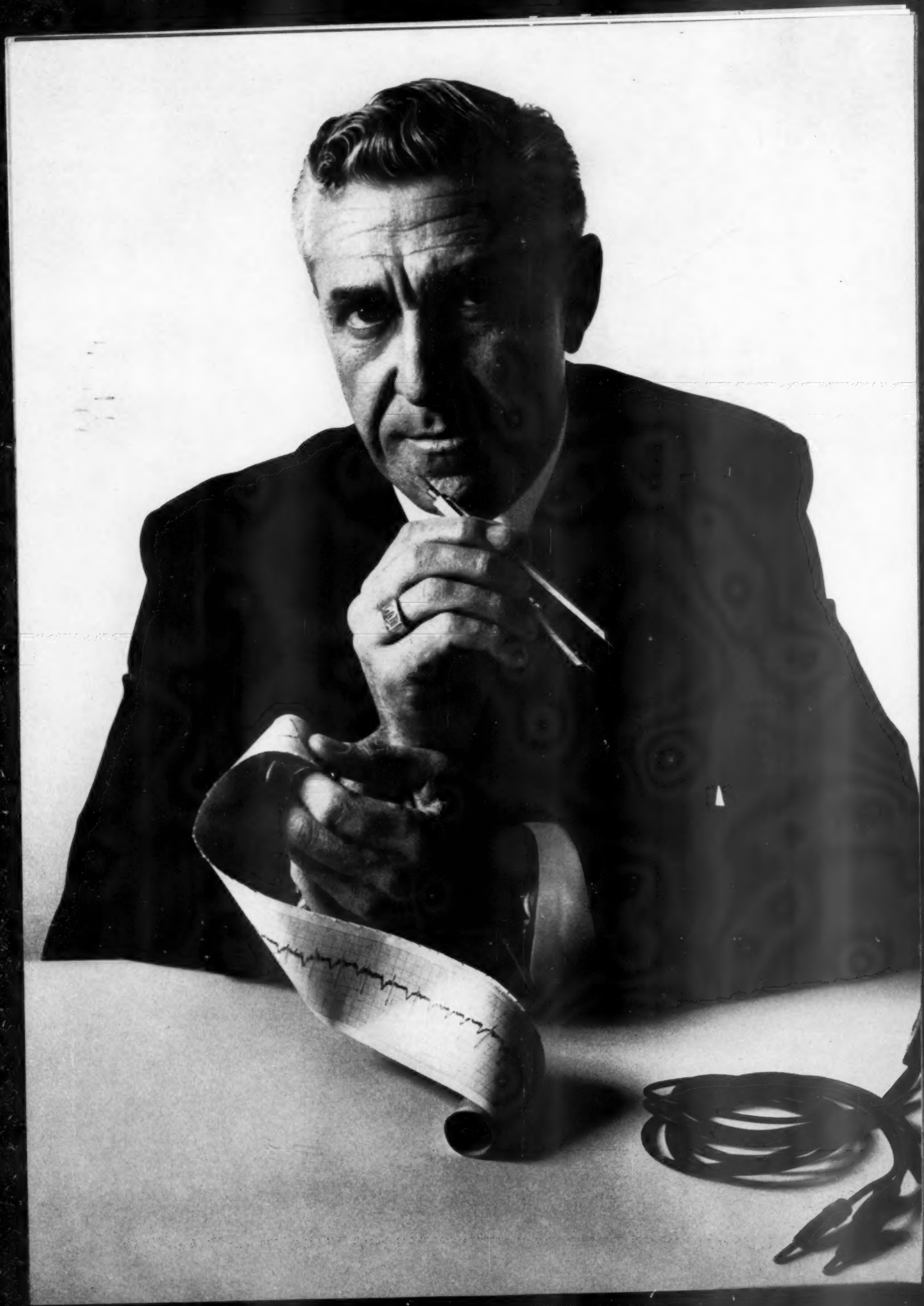
Dosage: One tablet 3 or 4 times a day is adequate for most patients. However, some require up to six tablets per day, whereas others respond adequately to as little as 1 tablet per day*

Composition: Each tablet contains sodium diethylbarbiturate 45 mg., sodium phenylethylbarbiturate 15 mg., sodium isobutylallylbarbiturate 25 mg., scopolamine hydrobromide 0.08 mg., dihydroergotamine methanesulfonate 0.16 mg.

1. Scheifley, C. H.: Proc. Staff Meet. Mayo Clin. 34:408 (Aug. 19) 1959.
2. Davanloo, H.: Am. J. of Psychiat. 117:740 (Feb.) 1961.

ORIGINAL RESEARCH SERVING THE PHYSICIAN

SANDOZ



Can we measure the patient's comfort?

The physician can measure activity of the heart by means of electrocardiography. But he has no instrument—no objective test—for measuring comfort.

For this, he must depend upon his own powers of observation and the patient's own description of how he feels.

Because these are, admittedly, subjective criteria, the validity of results hinges entirely on the experience and objectivity of the investigators involved.

Such well-qualified clinicians have reported that a new corticosteroid developed in research laboratories of Upjohn actually raises the level of relief obtainable with this type of therapy.

This difference cannot be "proved." It must be seen. And the only practical way for you to do this is to evaluate this new drug critically in your own practice. Please do, at your first opportunity. We are confident that you will be glad you did.

The new corticosteroid from Upjohn research

Alphadrol*

Each tablet contains Alphadrol (fluprednisolone) 0.75 mg. or 1.5 mg. Supplied in bottles of 25 and 100.

The anti-inflammatory activity of Alphadrol is comparable to the best effects obtained in current practice. Results obtained with Alphadrol have been such as to warrant classifying it among the most efficient steroids now available.

More than twice as potent as prednisolone, Alphadrol exhibits no new or bizarre side effects. Salt retention, edema or hypertension, potassium loss, anorexia, muscle weakness or muscle wasting, excessive appetite, abdominal cramping, or increased abdominal girth have not been a problem.

Indications and effects

The benefits of Alphadrol (anti-inflammatory, antiallergic, antirheumatic, antileukemic, antihemolytic) are indicated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

Precautions and contraindications

Patients on Alphadrol will usually experience dramatic relief *without* developing such possible steroid side effects as gastrointestinal intolerance, weight gain or weight loss, edema, hypertension, acne or emotional imbalance.

As in all corticotherapy, however, there are certain precautions to be observed. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates careful control in the use of steroids. Like all corticosteroids, Alphadrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

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June, 1961

The Upjohn Company, Kalamazoo, Michigan Upjohn

Unquestioned therapeutically

...long established clinically

TRISEM

SUSPENSION (chocolate-flavored)

For the many bacterial infections that respond promptly to triple sulfonamide therapy, Trisem presents a preferred formula.

Each 5 cc. contains, in a pleasant, chocolate-flavored vehicle:

Sulfamerazine (microcrystalline)	0.167 Gm. (2 3/5 gr.)
Sulfadiazine (microcrystalline)	0.167 Gm. (2 3/5 gr.)
Sulfamethazine (microcrystalline)	0.167 Gm. (2 3/5 gr.)

Each 5 cc. (1 tsp.) provides 0.5 Gm. total sulfonamides.

Each 15 cc. (1 tbsp.) provides 1.5 Gm. total sulfonamides.

ADVANTAGES

- **wide patient acceptability**
- **unquestioned therapeutic value**
- **high index of safety**
- **broad antibacterial spectrum**
- **provides high blood levels promptly**
- **economical for the patient**

Many physicians prefer to use the sulfonamides to control bacterial infections because resistant organisms rarely develop. Nor, as with some broad spectrum therapy, is there the complication of such after-effects as moniliasis.

PACKAGING: In pint and gallon bottles.

THE S. E. MASSENGILL COMPANY

BRISTOL, TENNESSEE

New York Kansas City San Francisco

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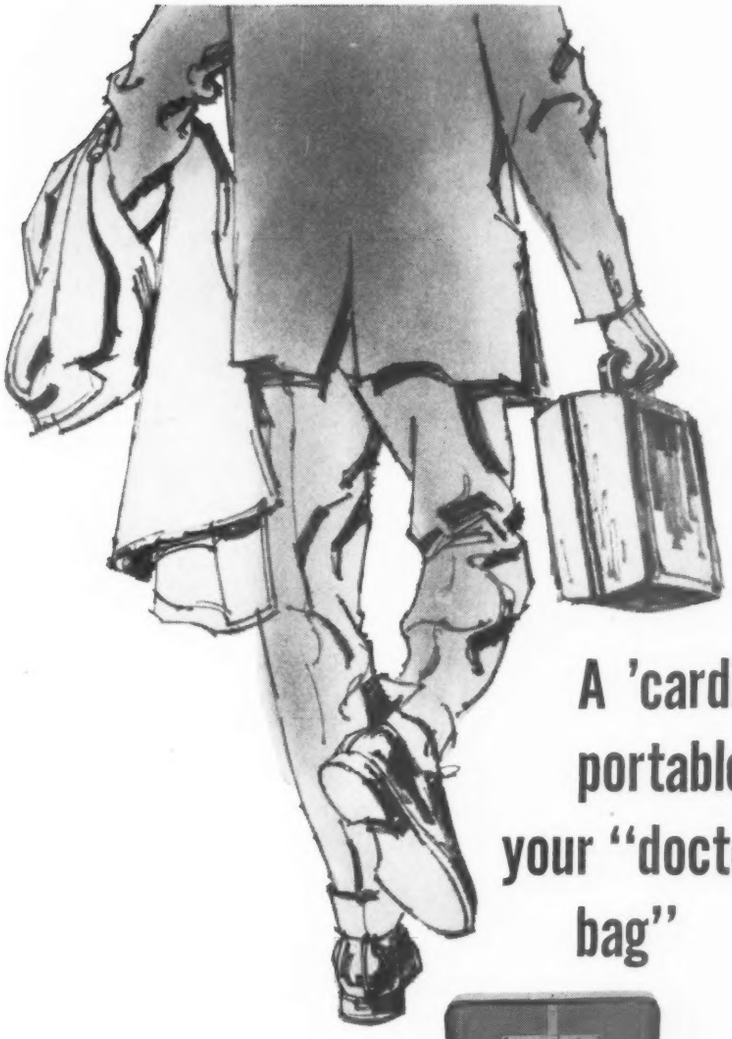


A 'cardiograph, portable as your "doctor's bag"

IT'S easy to take the Sanborn "300 Visette®" along on your house calls because it is compact and weighs only 18 pounds, including all accessories. Modern electronics — transistors and printed circuits — make it rugged to withstand the wear and tear on a portable instrument. Yet even with such durability and compactness, there has been no sacrifice in accuracy, dependability, and performance.

In addition to the portable model, Sanborn also offers the "100 Viso", a handsome desk-top ECG with two speeds, three recording sensitivities and provision for recording and monitoring other phenomena. Its mobile counterpart, the "100M Viso", is easily rolled to the patient's bedside in hospitals and clinics.

Ask your Sanborn Branch Office or Service Agency for complete information on the no-obligation 15-day trial period and convenient time payments. **Medical Division, SANBORN COMPANY, 175 Wyman St., Waltham 54, Mass.**

Sanborn service lasts long after the sale . . . from people who *know* your ECG and value *your* satisfaction.

Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltrate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: **1.** Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

CML-3619

Miltrate®

Miltown® (meprobamate) + PETN

WALLACE LABORATORIES / *Cranbury, N. J.*

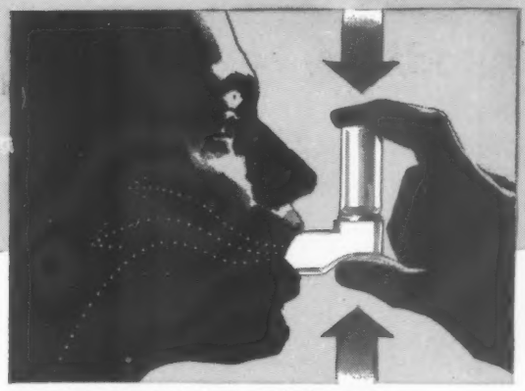
ASTHMA RELIEF *in seconds*

MEDIHALER®

the most effective anti-asthmatics...

administered in the most effective manner...

simplest and most convenient for the patient...



Available with either of the two outstanding bronchodilators

MEDIHALER-ISO®

Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each automatically measured dose contains 0.075 mg. isoproterenol.

MEDIHALER-EPI®

Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each automatically measured dose contains 0.15 mg. epinephrine.

Usual precautions for administration of isoproterenol and epinephrine should be observed.

Riker Northridge, California

Everyday practice report:
Following initial clinical investigational work, Forhistal was sent to physicians throughout the country for evaluation as an antiallergic and antipruritic agent in everyday practice. Results in 4026 cases have now been analyzed. In 2260 cases in which a comparison was made, Forhistal was judged better than previous therapy in 7 out of 10 patients. Information about the investigational work done previously is being mailed to you separately and is also available on request.

SUPPLIED: *Tablets*, 1 mg. (pale orange, scored). *Lontabs*, 2.5 mg. (orange). *Syrup* (pink), containing 1 mg. Forhistal maleate per 5-ml. teaspoon. *Pediatric Drops* (pink), containing 0.5 mg. Forhistal maleate per 0.6 ml.

For complete information about Forhistal (including dosage, cautions, and side effects), see Physicians' Desk Reference or write CIBA, Summit, N.J.

FORHISTAL® maleate
(dimethpyrindene maleate CIBA)
LONTABS® (long-acting tablets CIBA)

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SUMMIT, NEW JERSEY

Forhistal®
rated better than previous therapy in 7 cases out of 10

Forhistal Lontabs® for greater convenience, smoother response, prolonged action.

2/ 2910MK-2